

Alain Turck, Nelly Plé, Paméla Pollet, Ljubica Mojovic,
Jack Duflos and Guy Quéguiner*

INSA-IRCOF, Laboratoire de Chimie Organique Fine et Hétérocyclique,
URA 1429, B.P. 08, 76131 Mont St Aignan, France

Received June 24, 1996

The metalation of thioethers, methyl and phenyl sulfoxides and sulfones of pyrazine and pyridazine has been performed. Methyl sulfoxides and sulfones were first metalated on the methyl group. The *ortho* directing effect of thioethers, sulfoxides and sulfones have been compared with the methoxy group. The sulfoxides were shown to be very good *ortho* directing groups.

J. Heterocyclic Chem., 34, 621 (1997).

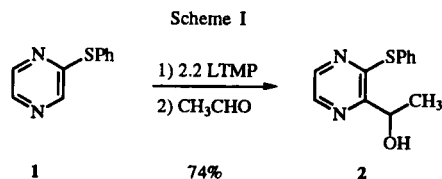
Introduction.

In aromatic systems some sulfur derivatives have been used as useful *ortho* directing groups for the metalation reaction: thioethers, sulfoxides, sulfones, sulfonic esters and sulfonamides [1-6]. These *ortho* directing groups have been used with success in the pyridine series [7,8] but to our knowledge, there are only two publications [9,10] dealing with the metalation directed by sulfur derivatives (thioethers) in the diazine series. In continuation of our studies on the metalation of diazines we tested the use of thioethers, sulfoxides and sulfones as *ortho* directing groups for pyrazines and pyridazines. Their efficiency as *ortho* directing groups have been evaluated in comparison with the methoxy group which is a good directing group in these series [11]. The metalation reaction has been followed by reaction with good electrophiles: acetaldehyde or/and benzaldehyde.

Results [18].

Metalation of Thioethers.

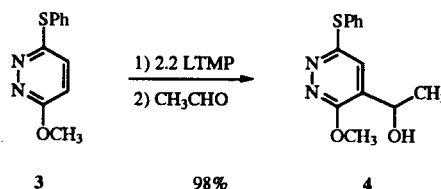
The metalation of 2-methylthiopyrazine has been described by Ward and Merritt [9] who obtained a good yield (76%). We tested the metalation of 2-phenylthiopyrazine 1 followed by reaction with acetaldehyde (Scheme I).



In the pyridazine series the 3,6 disubstituted derivatives are easily prepared from commercial 3,6-dichloropyridazine, so 3-methoxy-6-phenylthiopyridazine 3 was tested. The presence of a methoxy group in the 6 position allowed us to compare the two *ortho* directing groups (Scheme II).

The sole isolated product resulted from a regioselective metalation *ortho* to the methoxy group.

Scheme II



Metalation of Sulfoxides.

The sulfoxides were prepared from the corresponding thioethers by selective oxidation [12-15]. The metalation of 2-phenylsulfinylpyrazine was unsuccessful and no starting material was recovered. This failure may be explained by the good leaving group properties of the phenylsulfinyl moiety. In the pyridine series, Furokawa *et al* [16-17] achieved the cleavage of phenylsulfinylpyridines with Grignard reagents or lithio derivatives in order to prepare pyridine derivatives. To avoid this reaction a weaker leaving group was tested, the methylsulfinyl group (Scheme III, Table I).

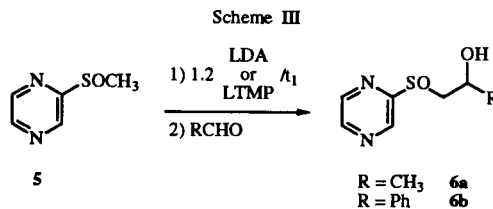
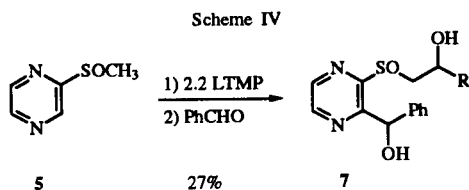


Table I

Metalating agent	Reaction time minutes	Electrophile	Product	Yield	Ratio of diastereoisomers
LTMP	15	PhCHO	6b	33%	75/25
LTMP [a]	30	PhCHO	6b	22%	64/36
LTMP	30	CH ₃ CHO	6a	50%	60/40
LDA	30	PhCHO	6b	62%	54/46
LDA	30	CH ₃ CHO	6a	51%	53/47

[a] 21% of **7** was also recovered.

The metalation took place on the methyl group instead of the aromatic ring, as was also noticed for methylsulfinylpyridines [16]. The greater acidity of the ring hydrogens in the diazine series in comparison with the pyridines could have favoured a ring metalation instead of the side chain reaction. Compounds **6a,b** have two chiral centers: the sulfoxide group and the carbon bearing the hydroxy group, this gave diastereoisomers and their ratio have been evaluated by their nmr spectra. With an excess of LTMP (2.2 equivalents) compound **7** was isolated, thus a ring metalation *ortho* to the sulfoxide group occurred (Scheme IV).



In the pyridazine series, lithiation of 3-phenylsulfinyl-6-methoxy-1,2,3,4-tetrahydropyridazine **8** was performed with a two fold excess of lithium 2,2,6,6-tetramethylpiperidide (LTMP) or lithium diisopropylamide (LDA) as metalating agent followed by reaction with various electrophiles (Scheme V, Table II).

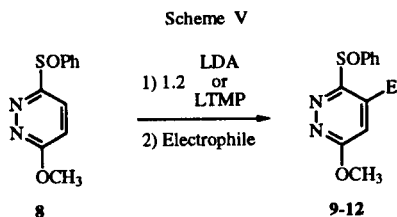
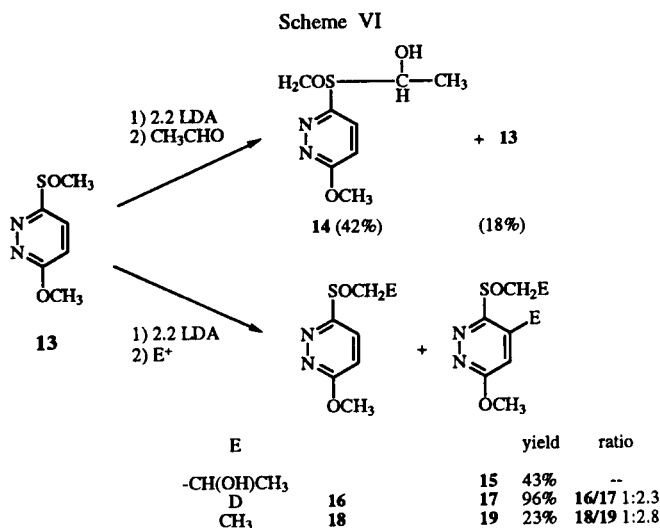


Table II

Metalating agent	Electrophile	Product	Yield	Ratio of diastereoisomers
LTMP	CH ₃ CHO	9	78%	75/25
LDA	CH ₃ CHO	9	78%	65/35
LTMP	(CH ₃) ₂ CHCHO	10	71%	55/45
LDA	(CH ₃) ₂ CHCHO	10	90%	64/36
LTMP	PhCHO	11	65%	60/40
LDA	PhCHO	11	78%	60/40
LTMP	ICH ₃	12	55%	
LDA [a]	ICH ₃	12	64%	

[a] 14% of 3-phenylsulfinyl-4,5-dimethyl-6-methoxy-1,2,3,4-tetrahydropyridazine was obtained.

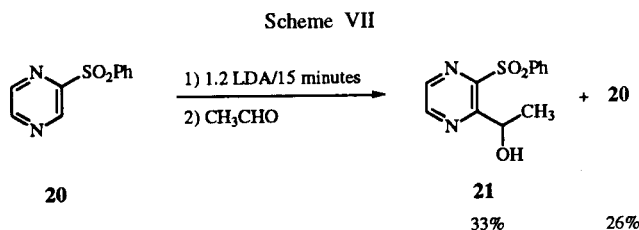
In all experiments a regioselective metalation was observed *ortho* to the phenylsulfinyl group (4 position) no 5 isomer could be observed. Diastereoisomers were obtained in various ratios. A methylsulfinyl group was tested and we observed that the first metalation took place on the methyl group like in the pyrazines (Scheme VI):



Compounds **16**, **17**, **18** and **19** could not be separated and their ratios were determined from their nmr spectra. The yield of deuterated products **16** and **17** (96%) indicated that the metalation was complete and the moderate yields obtained when other electrophiles were used (acetaldehyde and iodomethane) indicated that the reaction with the electrophile was the limiting step. Product **14** also gave diastereoisomers in a 30/70 proportion and the three chiral centers of **15** lead to complex signals in the ¹H nmr spectrum.

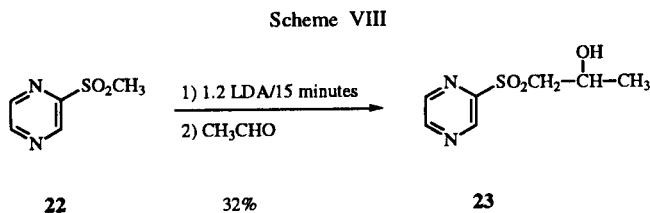
Metalation of Sulfones.

In contrast to the sulfoxide analogue, 2-phenylsulfonylpyridazine **20** could be metalated (Scheme VII).



The use of lithium 2,2,6,6-tetramethylpiperidide as metalating agent gave a lower yield (10%). The metalation time was varied and a time of 15 minutes gave the best results.

2-Methylsulfonylpyridazine **22** was metalated and the metalation occurred on the methyl group as for the methylsulfinyl derivatives. A typical experiment is given below (Scheme VIII).



In the pyridazine series 3-phenylsulfonyl-6-methoxy-pyridazine **24** was metalated (Scheme IX, Table III).

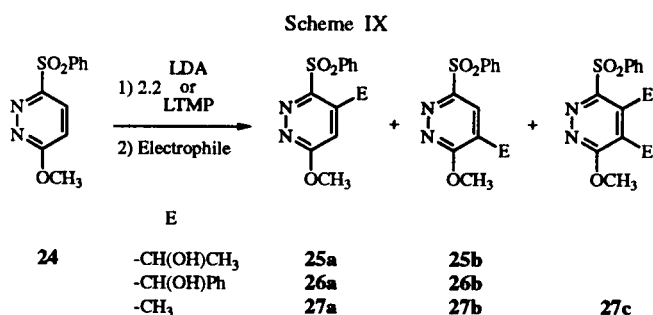


Table III

Metalating agent	Electrophile	Compound	Yield	Ratio		
				%a	%b	%c
LTMP	CH ₃ CHO	25	56%	77%	23%	-
LDA	CH ₃ CHO	25	58%	70%	30%	-
LTMP	PhCHO	26	68%	78%	22%	-
LDA	PhCHO	26	86%	70%	30%	-
LTMP	ICH ₃	27	61%	55%	15%	30%
LDA	ICH ₃	27	66%	50%	20%	30%

The ratio of the a,b,c isomers were determined with their ¹H nmr spectra. When aldehydes were used as electrophiles, no disubstituted isomer of type c was isolated. With iodomethane a 30% amount of that isomer was present. In all experiments the relative proportions of isomers a and b were remarkably constant with the metalating agent: 78/22 with lithium 2,2,6,6,-tetramethylpiperidide and 70/30 with lithium diisopropylamide.

The use of a methylsulfonyl group led to metalation on the methyl group (Scheme X).

When lithium diisopropylamide was used as the metalating agent it was possible to perform a selective metalation on the methylsulfonyl group with medium yield (60%).

The use of a stronger metalating agent (lithium 2,2,6,6,-tetramethylpiperidide) afforded a mixture of products **29**, and **30**. Reaction of the lithio derivative with deuterated ethanol gave, beside compound **31a**, the two *ortho* isomers **31b** and **31c**. The isomer **31b** *ortho* to the methylsulfonyl group was the more abundant as for the phenylsulfonyl group (Table III).

Discussion.

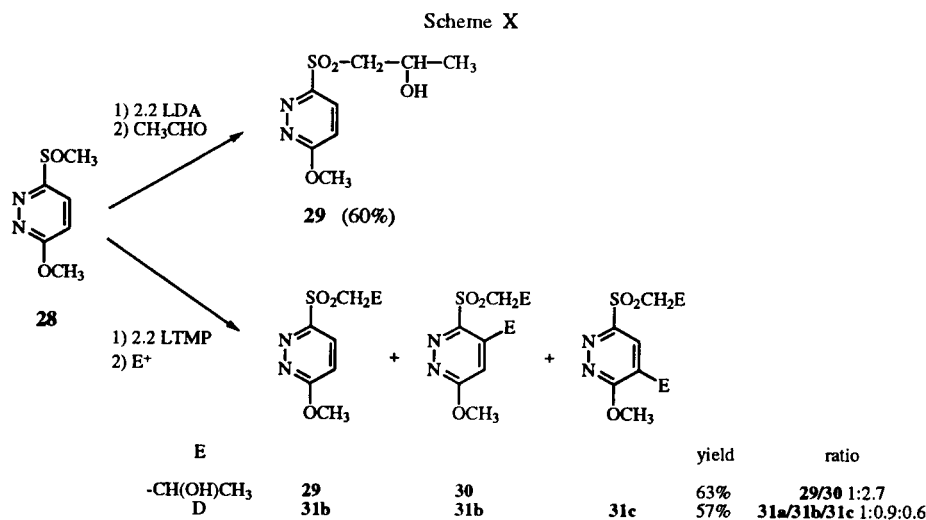
The phenylthio moiety was a weak *ortho* directing group for the metalation of 3-methoxy-6-phenylthiopyridazine as can be seen in Scheme II, the metalation took place only in *ortho* to the methoxy group. If 2-phenylthio or 2-methylthiopyridazine gave good yields (Scheme I) this was due to the strong acidity of the 3 hydrogen which is between the phenylthio group and the ring nitrogen.

For 2-phenylsulfinylpyridazine **5** we could not obtain an *ortho* metalation and it could be assumed that a nucleophilic substitution of the phenylsulfinyl group was the main reaction. In the case of 3-methoxy-6-phenylsulfinylpyridazine **13** the electron donating effect of the methoxy group disfavoured the nucleophilic substitution and the metalation could take place with good yields. The phenylsulfinyl group was a very good *ortho* directing group: when it was opposed to a methoxy group, the metalation was regioselective. This result had been also observed with the *t*-butylsulfinyl group in the benzene series [8].

When methylsulfinyl or methylsulfonyl groups were tested as *ortho* directing groups the first metalation took place on the methyl group and this reaction could be used to functionalize the side chain.

The phenylsulfonyl group was a good *ortho* directing group but weaker than the phenylsulfinyl group.

These results show that some sulfur *ortho* directing groups could be usefully used for the metalation of diazines and this prompts us to investigate further this topic.



EXPERIMENTAL

Melting points were determined on a Kofler hot-stage apparatus. The ^1H nmr spectra were recorded in deuteriochloroform or in deuterated dimethyl sulfoxide on a Bruker AC 200 (200 MHz) spectrometer. Microanalyses were performed on a Carlo Erba CHNOS 1160 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 10 μ (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 (THF 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 THF (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 THF 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 THF (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-[(1-Hydroxy)ethyl]-2-phenylthiopyrazine (2).

Metalation of 1 (0.21 g, 1.1 mmoles) according to the general procedure with *n*-butyllithium 2.5 *M* (0.98 ml, 2.4 mmoles) and 2,2,6,6-tetramethylpiperidine (0.41 ml, 2.5 mmoles), $t_1 = 60$ minutes then reaction with acetaldehyde (1 ml, 18 mmoles), $t_2 = 60$ minutes gave after purification by column chromatography on silica gel with a mixture of dichloromethane/ethyl acetate (8:2) as an eluent a yellow powder of 2 (0.19 g, 74%), mp 81°; ^1H nmr (deuteriochloroform): δ 1.50 (d, 3H, $J_{\text{CH}_3\text{-CH}} = 6.0$ Hz, CH_3), 4.13 (s, 1H, OH), 5.16 (q, 1H, $J_{\text{CH}_3\text{-CH}} = 6.0$ Hz, CH), 7.40 (m, 5H, Ph), 8.16 (s, 2H, $\text{H}_5 + \text{H}_6$).

Anal. Calcd. for $\text{C}_{12}\text{H}_{12}\text{N}_2\text{OS}$: C, 62.10; H, 5.17; N, 12.10. Found: C, 62.1; H, 5.3; N, 12.0.

4-[(1-Hydroxy)ethyl]-3-methoxy-6-phenylthiopyridazine (4).

Metalation of 3 (0.47 g, 2.1 mmoles) according to the general procedure with *n*-butyllithium 2.5 *M* (1.90 ml, 4.7 mmoles) and 2,2,6,6-tetramethylpiperidine (0.84 ml, 4.9 mmoles), $t_1 = 60$ minutes then reaction with acetaldehyde (1 ml, 18 mmoles), $t_2 = 60$ minutes gave after purification by column chromatography on silica gel with a mixture of dichloromethane/ethyl acetate (8:2) as an eluent a yellow oil of 4 (0.55 g, 98%); ^1H nmr (deuteriochloroform): δ 1.37 (d, 3H, $J_{\text{CH}_3\text{-CH}} = 6.0$ Hz, CH_3), 4.07 (s, 3H, OCH_3), 4.97 (q, 1H, $J_{\text{CH}_3\text{-CH}} = 6.0$ Hz, CH), 7.43 (m, 6H, Ph + H_5).

Anal. Calcd. for $\text{C}_{13}\text{H}_{14}\text{N}_2\text{O}_2\text{S}$: C, 59.50; H, 5.34; N, 10.70. Found: C, 59.3; H, 5.7; N, 10.8.

2-[(2-Hydroxy)propylsulfinyl]pyrazine (6a).

Metalation of 5 (0.20 g, 1.41 mmoles) according to the general procedure with *n*-butyllithium 1.6 *M* (1.06 ml, 1.69 mmoles) and diisopropylamine (0.24 ml, 1.69 mmoles), $t_1 = 30$ minutes then reaction with acetaldehyde (1 ml, 18 mmoles), $t_2 = 30$ minutes gave after purification by column chromatography on silica gel with ethyl acetate as an eluent an orange oil of 6a (0.10 g, 51%). The proportion of the two diastereoisomers were determined by ^1H nmr and are 53/47 (6aA, 6aB); ^1H nmr (deuteriochloroform): δ 1.24 (d, 3H, $J_{\text{CH}_3\text{-CH}} = 6.1$ Hz, CH_3^{A}), 1.30 (d, 3H, $J_{\text{CH}_3\text{-CH}} = 6.1$ Hz, CH_3^{B}), 3.13 (m, 2H, CH_2), 3.78 (s, 1H, OH), 4.33 (m, 1H, CH), 4.47 (m, 1H, CH), 8.55 (m, 1H, $\text{H}_5^{\text{(A+B)}}$), 8.64 (d, 1H, $J_{5-6} = 2.0$ Hz, H_6^{B}), 8.67 (d, 1H, $J_{5-6} = 2.0$ Hz, H_6^{A}), 9.10 (s, 1H, H_3^{B}), 9.14 (s, 1H, H_3^{A}); ir: 3382 cm^{-1} , ν OH; 1053, 1014 cm^{-1} , ν S=O.

Anal. Calcd. for $\text{C}_7\text{H}_{10}\text{N}_2\text{O}_2\text{S}$: C, 45.20; H, 5.42; N, 15.06. Found: C, 44.9; H, 5.5; N, 15.0.

2-[(2-Phenyl-2-hydroxy)ethylsulfinyl]pyrazine (6b).

Metalation of 5 (0.20 g, 1.41 mmoles) according to the general procedure with *n*-butyllithium 1.6 *M* (1.06 ml, 1.69 mmoles) and diisopropylamine (0.24 ml, 1.69 mmoles), $t_1 = 30$ minutes then reaction with benzaldehyde (0.17 ml, 1.69 mmoles), $t_2 = 60$ minutes gave after purification by column chromatography on silica gel with a mixture of ethanol/ethyl acetate (1:9) as an eluent a pale orange powder of 6b (0.21 g, 62%). Proportion of the two diastereoisomers were determined by ^1H nmr and are 54/46 (6bA, 6bB), mp 132°; ^1H nmr (deuteriochloroform): δ 3.42 (d, 2H, $J_{\text{CH}_2\text{-CH}} = 2.0$ Hz, CH_2^{B}), 3.46 (d, 2H, $J_{\text{CH}_2\text{-CH}} = 2.0$ Hz, CH_2^{A}), 3.71 (s, 1H, OH^{A}), 4.30 (s, 1H, OH^{B}), 5.28 (m, 1H, CH^{B}), 5.48 (m, 1H, CH^{A}), 7.32 (m, 5H, Ph), 8.56 (d, 1H, $J_{5-6} = 2.3$ Hz, H_5 or 6^{A}), 8.59 (d, 1H, $J_{5-6} = 2.3$ Hz, H_5 or 6^{B}), 8.65 (d, 1H, $J_{5-6} = 2.3$ Hz, H_5 or 6^{B}), 8.70 (d, 1H, $J_{5-6} = 2.3$ Hz, H_5 or 6^{A}), 9.15 (d, 1H, $J_{3-6} = 1.0$ Hz, H_3^{A}), 9.20 (d, 1H, $J_{3-6} = 1.0$ Hz, H_3^{B}); ir: 3302 cm^{-1} , ν OH; 1395, 1044 cm^{-1} , ν S=O.

Anal. Calcd. for $\text{C}_{12}\text{H}_{12}\text{N}_2\text{O}_2\text{S}$: C, 58.12; H, 4.88; N, 11.29. Found: C, 57.7; H 4.9; N, 11.3.

3-Hydroxybenzyl-2-[(2-phenyl-2-hydroxy)ethylsulfinyl]pyrazine (7).

Metalation of 5 (0.20 g, 1.41 mmoles) according to the general procedure with *n*-butyllithium 1.6 *M* (1.93 ml, 3.10 mmoles) and 2,2,6,6-tetramethylpiperidine (0.52 ml, 3.10 mmoles), $t_1 = 30$ minutes then reaction with benzaldehyde (0.17 ml, 1.69 mmoles), $t_2 = 60$ minutes gave after purification by column chromatography on silica gel with a mixture of ethanol/ethyl acetate (1:9) as an eluent an orange oil of 7 (0.13 g, 27%); ^1H nmr (deuteriochloroform): δ 3.28-3.48 (m, 2H, CH_2), 4.24 (s, 1H, OH), 5.10 (s, 1H, OH), 5.31 (m, 1H, CH-CH_2), 6.21 (s, 1H, CH-OH), 6.29 (s, 1H, CH-OH), 7.28 (m, 10H, Ph + Ph), 8.56 (m, 1H, H_5 or 6), 8.64 (m, 1H, H_5 or 6).

Anal. Calcd. for $\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}_3\text{S}$: C, 64.46; H, 5.12; N, 7.91. Found: C, 64.3; H, 5.5; N, 8.2.

4-[(1-Hydroxy)ethyl]-6-methoxy-3-phenylsulfinylpyridazine (9).

Metalation of **8** (0.20 g, 0.85 mmole) according to the general procedure with *n*-butyllithium 1.6 *M* (1.12 ml, 1.87 mmoles) and 2,2,6,6-tetramethylpiperidine (0.33 ml, 1.87 mmoles), $t_1 = 35$ minutes then reaction with acetaldehyde (1 ml, 18 mmoles), $t_2 = 60$ minutes gave after purification by column chromatography on silica gel with a mixture of dichloromethane/ethyl acetate (5:5) as an eluent an orange oil of **9** (0.18 g, 78%). Proportion of diastereoisomers were determined by ^1H nmr and are 75/25 (**9A**, **9B**); ^1H nmr (deuteriochloroform): δ 1.17 (d, 3H, $\text{J}_{\text{CH}_3\text{-CH}} = 6.5$ Hz, CH_3^{A}), 1.43 (d, 3H, $\text{J}_{\text{CH}_3\text{-CH}} = 6.5$ Hz, CH_3^{B}), 4.04 (s, 3H, OCH_3^{B}), 4.07 (s, 3H, OCH_3^{A}), 4.48 (s, 1H, OH^{B}), 4.99 (s, 1H, OH^{A}), 5.14 (q, 1H, $\text{J}_{\text{CH-CH}_3} = 6.5$ Hz, CH^{A}), 5.30 (q, 1H, $\text{J}_{\text{CH-CH}_3} = 6.5$ Hz, CH^{B}), 7.01 (s, 1H, H_5^{B}), 7.10 (s, 1H, H_5^{A}), 7.38 (m, 3H, Ph), 7.62 (m, 2H, Ph).

Anal. Calcd. for $\text{C}_{13}\text{H}_{14}\text{N}_2\text{O}_3\text{S}$: C, 56.11; H, 5.03; N, 10.07. Found C, 56.1; H, 5.3; N, 9.8.

4-[(1-Hydroxy)isopropyl]-6-methoxy-3-phenylsulfanylpyridazine (**10**).

Metalation of **8** (0.20 g, 0.85 mmole) according to the general procedure with *n*-butyllithium 1.6 *M* (1.12 ml, 1.87 mmoles) and 2,2,6,6-tetramethylpiperidine (0.33 ml, 1.87 mmoles), $t_1 = 35$ minutes then reaction with isobutyraldehyde (0.09 ml, 1.02 mmoles), $t_2 = 60$ minutes gave after purification by column chromatography on silica gel with a mixture of dichloromethane/ethyl acetate (5:5) as an eluent a yellow oil of **10** (0.18 g, 71%). Proportion of the two diastereoisomers were determined by ^1H nmr and are 55/45 (**10A**, **10B**); ^1H nmr (deuteriochloroform): δ 0.55 (d, 3H, $\text{J}_{\text{CH}_3\text{-CH}} = 6.7$ Hz, CH_3), 0.78 (d, 3H, $\text{J}_{\text{CH}_3\text{-CH}} = 6.7$ Hz, CH_3), 0.85 (d, 3H, $\text{J}_{\text{CH}_3\text{-CH}} = 6.7$ Hz, CH_3), 0.87 (d, 3H, $\text{J}_{\text{CH}_3\text{-CH}} = 6.7$ Hz, CH_3), 1.84 (sex, 1H, $\text{J}_{\text{CH-CH}} = 6.9$ Hz, $\text{J}_{\text{CH-CH}_3} = 6.7$ Hz, CH^{A}), 2.00 (sex, 1H, $\text{J}_{\text{CH-CH}} = 6.9$ Hz, $\text{J}_{\text{CH-CH}_3} = 6.7$ Hz, CH^{B}), 4.04 (s, 3H, OCH_3^{B}), 4.07 (s, 3H, OCH_3^{A}), 4.11 (s, 1H, OH^{B}), 4.57 (s, 1H, OH^{A}), 4.64 (d, 1H, $\text{J}_{\text{CH-CH}} = 6.9$ Hz, CH-OH^{A}), 4.85 (d, 1H, $\text{J}_{\text{CH-CH}} = 6.9$ Hz, CH-OH^{B}), 6.96 (s, 1H, H_5^{A}), 7.03 (s, 1H, H_5^{B}), 7.39 (m, 3H, Ph), 7.65 (m, 2H, Ph).

Anal. Calcd. for $\text{C}_{15}\text{H}_{18}\text{N}_2\text{O}_3\text{S}$: C, 58.82; H, 5.90; N, 9.15. Found: C, 58.8; H, 5.9; N, 9.1.

4-[(1-Hydroxy)benzyl]-6-methoxy-3-phenylsulfanylpyridazine (**11**).

Metalation of **8** (0.20 g, 0.85 mmole) according to the general procedure with *n*-butyllithium 2.5 *M* (0.72 ml, 1.87 mmoles) and diisopropylamine (0.27 ml, 1.87 mmoles), $t_1 = 35$ minutes then reaction with benzaldehyde (0.10 ml, 1.02 mmoles), $t_2 = 60$ minutes gave after purification by column chromatography on silica gel with a mixture of dichloromethane/ethyl acetate (5:5) as an eluent a yellow oil of **11** (0.23 g, 78%). Proportion of the two diastereoisomers were determined by ^1H nmr and are 60/40 (**11A**, **11B**); ^1H nmr (deuteriochloroform): δ 4.10 (s, 3H, OCH_3), 4.65 (s, 1H, OH^{B}), 5.28 (s, 1H, OH^{A}), 6.15 (s, 1H, CH^{A}), 6.31 (s, 1H, CH^{B}), 6.52 (s, 1H, H_5^{A}), 6.95 (s, 1H, H_5^{B}), 7.35 (m, 10 H, Ph + Ph); ir: 3334 cm^{-1} , ν OH; 1019 cm^{-1} , ν S=O.

Anal. Calcd. for $\text{C}_{18}\text{H}_{16}\text{N}_2\text{O}_3\text{S}$: C, 63.52; H, 4.70; N, 8.23. Found C, 63.7; H 5.0; N, 7.9.

6-Methoxy-4-methyl-3-phenylsulfanylpyridazine (**12**).

Metalation of **8** (0.20 g, 0.85 mmole) according to the general procedure with *n*-butyllithium 1.6 *M* (1.17 ml, 1.88 mmoles) and diisopropylamine (0.27 ml, 1.88 mmoles), $t_1 = 30$ minutes

then reaction with methyl iodide (0.12 ml, 1.88 mmoles), $t_2 = 60$ minutes gave after purification by column chromatography on silica gel with a mixture of dichloromethane/ethyl acetate (5:5) as an eluent a yellow oil of two metalation products (0.16 g, 74%). Proportion of the two metalation products were determined by ^1H nmr and are **12** (86%) and 4,5-dimethyl-6-methoxy-3-phenylsulfanyl pyridazine (14%); after further purification by hplc (50 μl , $\lambda = 230$ nm) with a mixture of methanol/water (6:4) as an eluent a pure analytical sample of **12** have been obtained; ^1H nmr (deuteriochloroform): δ 2.33 (s, 3H, CH_3), 4.10 (s, 3H, OCH_3), 6.70 (s, 1H, H_5), 7.42 (m, 3H, Ph), 7.63 (m, 2H, Ph); ir: 3060 cm^{-1} , ν OH; 1168 cm^{-1} , ν S=O.

Anal. Calcd. for $\text{C}_{12}\text{H}_{12}\text{N}_2\text{O}_2\text{S}$: C, 58.12; H, 4.88; N, 11.29. Found C, 58.2; H, 5.0; N, 11.3.

3-[(2-Hydroxy)propylsulfanyl]-6-methoxy pyridazine (**14**).

Metalation of **13** (0.08 g, 0.46 mmole) according to the general procedure with *n*-butyllithium 1.6 *M* (0.35 ml, 0.56 mmole) and diisopropylamine (0.08 ml, 0.56 mmole), $t_1 = 30$ minutes then reaction with acetaldehyde (1 ml, 18 mmoles), $t_2 = 30$ minutes gave after purification by column chromatography on silica gel with a mixture of ethanol/ethyl acetate (1:9) as an eluent a pale yellow powder of **14** (0.04 g, 42%). Proportion of two diastereoisomers were determined by ^1H nmr and are 70/30 (**14A**, **14B**), mp 67°; ^1H nmr (deuteriochloroform): δ 1.27 (d, 3H, $\text{J}_{\text{CH}_3\text{-CH}} = 6.4$ Hz, CH_3^{A}), 1.34 (d, 3H, $\text{J}_{\text{CH}_3\text{-CH}} = 6.4$ Hz, CH_3^{B}), 3.09-3.39 (m, (2+1)H, $\text{CH}_2 + \text{OH}$), 4.08 (s, 1H, OH), 4.17 (s, 3H, OCH_3), 4.18 (s, 3H, OCH_3), 4.52 (m, 1H, CH), 7.21 (d, 1H, $\text{J}_{4,5} = 9.6$ Hz, H_5^{A}), 7.23 (d, 1H, $\text{J}_{4,5} = 9.6$ Hz, H_5^{B}), 8.01 (d, 1H, $\text{J}_{4,5} = 9.6$ Hz, H_4^{B}), 8.06 (d, 1H, $\text{J}_{4,5} = 9.6$ Hz, H_4^{A}).

Anal. Calcd. for $\text{C}_8\text{H}_{12}\text{N}_2\text{O}_3\text{S}$: C, 44.48; H, 5.60; N, 12.97. Found C 44.7; H 5.7; N, 12.7.

4-[(1-Hydroxy)ethyl]-3-[(2-hydroxy)propylsulfanyl]-6-methoxy pyridazine (**15**).

Metalation of **13** (0.10 g, 0.58 mmole) according to the general procedure with *n*-butyllithium 2.5 *M* (0.50 ml, 1.27 mmoles) and diisopropylamine (0.18 ml, 1.27 mmoles), $t_1 = 30$ minutes then reaction with acetaldehyde (1 ml, 18 mmoles), $t_2 = 30$ minutes gave after purification by column chromatography on silica gel with a mixture of ethanol/ethyl acetate (1:9) as an eluent an orange oil of **15** (0.07 g, 43%); ^1H nmr (deuteriochloroform): δ 1.32 (m, 3H, CH_3), 1.54 (m, 3H, CH_3), 3.06-3.59 (m, 2H, CH_2), 3.99 (s, 1H, OH), 4.14 (s, 3H, OCH_3), 4.43 (m, 1H, CH-CH_2), 5.16 (m, 1H, CH), 5.33 (m, 1H, CH), 7.06 (s, 1H, H_5), 7.14 (s, 1H, H_5); ir: 3357 cm^{-1} , ν OH; 1016 cm^{-1} , ν S=O.

Anal. Calcd. for $\text{C}_{10}\text{H}_{16}\text{N}_2\text{O}_4\text{S}$: C, 46.20; H, 6.20; N, 10.77. Found C, 46.5; H, 6.1; N, 10.6.

3-(Deuteriomethylsulfanyl)-6-methoxy pyridazine (**16**) and 3-(Deuteriomethylsulfanyl)-4-deuterio-6-methoxy pyridazine (**17**).

Metalation of **13** (0.10 g, 0.58 mmole) according to the general procedure with *n*-butyllithium 2.5 *M* (0.50 ml, 1.28 mmoles) and diisopropylamine (0.18 ml, 1.28 mmoles), $t_1 = 30$ minutes then reaction with ethyl alcohol-*d* (0.50 ml), $t_2 = 30$ minutes and chloride deuteride (0.3 ml), $t_2' = 10$ minutes gave a colorless oil of two metalation products **16** and **17** (0.10 g, 96%). Proportion of the two metalation products were determined by ^1H nmr and are **16** (30%) and **17** (70%); ^1H nmr (deuteriochloroform): δ 2.81 (d, 2H, $\text{J} = 0.8$ Hz, CH_2), 2.82 (d, 2H, $\text{J} = 0.8$ Hz, CH_2), 4.04 (s, 3H, OCH_3), 4.05 (s, 3H, OCH_3),

7.10 (s, 1H, H₅¹⁷), 7.11 (d, 1H, J₄₋₅ = 9.0 Hz, H₅¹⁶), 7.92 (d, 1H, J₄₋₅ = 9.0 Hz, H₄¹⁶).

3-Ethylsulfinyl-6-methoxy-pyridazine (**18**) and 3-Ethylsulfinyl-4-methyl-6-methoxy-pyridazine (**19**).

Metalation of **13** (0.15 g, 0.87 mmole) according to the general procedure with *n*-butyllithium 2.5 M (0.78 ml, 1.92 mmoles) and diisopropylamine (0.27 ml, 1.92 mmoles), t₁ = 30 minutes then reaction with methyl iodide (0.12 ml, 1.92 mmoles), t₂ = 30 minutes gave after purification by column chromatography on silica gel with a mixture of ethanol/ethyl acetate (1:9) as an eluent a brown oil of two metalation products **18**, **19** (0.04 g, 23%). Proportion of the two metalation products were determined by ¹H nmr and are **18** (22%) and **19** (78%); ¹H nmr (deuteriochloroform): δ 1.34 (t, 3H, J_{CH₃-CH₂} = 7.4 Hz, CH₃-CH₂), 2.60 (s, 3H, CH₃¹⁹), 3.36 (q, 2H, J_{CH₂-CH₃} = 7.4 Hz, CH₂-CH₃), 4.14 (s, 3H, OCH₃), 6.84 (s, 1H, H₅¹⁹), 7.20 (d, 1H, J₄₋₅ = 9.1 Hz, H₅¹⁸), 8.03 (d, 1H, J₄₋₅ = 9.1 Hz, H₄¹⁸)

3-[(1-Hydroxy)ethyl]-2-phenylsulfonylpyrazine (**21**).

Metalation of **20** (0.20 g, 0.91 mmole) according to the general procedure with *n*-butyllithium 1.6 M (1.25 ml, 2.00 mmoles) and 2,2,6,6-tetramethylpiperidine (0.33 ml, 2.00 mmoles), t₁ = 10 minutes then reaction with acetaldehyde (1 ml, 18 mmoles), t₂ = 60 minutes gave after purification by column chromatography on silica gel with a mixture of dichloromethane/ethyl acetate (8:2) as an eluent an orange oil of **21** (0.03 g, 10%); ¹H nmr (deuteriochloroform): δ 1.66 (d, 3H, J_{CH₃-CH} = 6.0 Hz, CH₃), 3.79 (s, 1H, OH), 5.89 (q, 1H, J_{CH-CH₃} = 6.0 Hz, CH), 7.64 (m, 3H, Ph), 8.05 (m, 2H, Ph), 8.47 (d, 1H, J₅₋₆ = 2.0 Hz, H_{5 or 6}), 8.71 (d, 1H, J₅₋₆ = 2.0 Hz, H_{5 or 6})

Anal. Calcd. for C₁₂H₁₂N₂O₃S: C, 54.54; H, 4.54; N, 10.60. Found C, 54.4; H, 4.8; N, 10.5.

2-[(2-Hydroxy)ethylsulfonyl]pyrazine (**23**).

Metalation of **22** (0.16 g, 0.99 mmole) according to the general procedure with *n*-butyllithium 1.6 M (0.74 ml, 1.18 mmoles) and diisopropylamine (0.17 ml, 1.18 mmoles), t₁ = 30 minutes then reaction with acetaldehyde (1 ml, 18 mmoles), t₂ = 30 minutes gave after purification by column chromatography on silica gel with a mixture of ethanol/ethyl acetate (5:95) as an eluent a brown oil of **23** (0.06 g, 32%); ¹H nmr (deuteriochloroform): δ 1.29 (d, 3H, J_{CH₃-CH} = 6.3 Hz, CH₃), 3.20 (s, 1H, OH), 3.54 (m, 2H, CH₂), 4.45 (m, 1H, CH), 8.72 (dd, J₅₋₆ = 2.0 Hz, J₃₋₆ = 1.6 Hz, H₆), 8.88 (d, 1H, J₅₋₆ = 2.0 Hz, H₅), 9.29 (d, 1H, J₃₋₆ = 1.6 Hz, H₃); ir: 3284 cm⁻¹, ν OH, 1399, 1112 cm⁻¹, ν S=O.

Anal. Calcd. for C₇H₁₀N₂O₃S: C, 41.62; H, 4.99; N, 13.87. Found: C, 41.4; H, 5.0; N, 13.8.

4-[(1-Hydroxy)ethyl]-6-methoxy-3-phenylsulfonylpyridazine (**25a**) and 5-[(1-Hydroxy)ethyl]-6-methoxy-3-phenylsulfonylpyridazine (**25b**).

Metalation of **24** (0.21 g, 0.86 mmole) according to the general procedure with *n*-butyllithium 1.6 M (1.18 ml, 1.89 mmoles) and 2,2,6,6-tetramethylpiperidine (0.32 ml, 1.89 mmoles), t₁ = 35 minutes then reaction with acetaldehyde (1 ml, 18 mmoles), t₂ = 60 minutes gave after purification by column chromatography on silica gel with a mixture of dichloromethane/ethyl acetate (8:2) as an eluent a yellow oil of two metalation isomers **25a** and **25b** (0.14 g, 56%). Proportion of the two metalation isomers were

determined by ¹H nmr and are **25a** (77%) and **25b** (23%); ¹H nmr (deuteriochloroform): δ 1.41 (d, 3H, J_{CH₃-CH} = 6.4 Hz, CH₃^b), 1.57 (d, 3H, J_{CH₃-CH} = 6.4 Hz, CH₃^a), 3.69 (s, 1H, OH^{a+b}), 4.07 (s, 3H, OCH₃^a), 4.14 (s, 3H, OCH₃^b), 4.99 (q, 1H, J_{CH-CH₃} = 6.4 Hz, CH^b), 5.78 (q, 1H, J_{CH-CH₃} = 6.4 Hz, CH^a), 7.38 (s, 1H, H₅^a), 7.70 (m, 3H, Ph), 8.01 (m, 2H, Ph), 8.29 (s, 1H, H₄^b).

Anal. Calcd. for C₁₃H₁₄N₂O₄S: C, 53.10; H, 4.80; N, 9.50. Found: C, 53.2; H, 4.9; N, 9.3.

4-(Hydroxybenzyl)-6-methoxy-3-phenylsulfonylpyridazine (**26a**) and 5-(Hydroxybenzyl)-6-methoxy-3-phenylsulfonylpyridazine (**26b**).

Metalation of **24** (0.21 g, 0.86 mmole) according to the general procedure with *n*-butyllithium 2.5 M (0.75 ml, 1.89 mmoles) and diisopropylamine (0.27 ml, 1.89 mmoles), t₁ = 35 minutes then reaction with benzaldehyde (0.11 ml, 1.03 mmoles), t₂ = 60 minutes gave after purification by column chromatography on silica gel with a mixture of dichloromethane/ethyl acetate (8:2) as an eluent a pale yellow powder of two metalation isomers **26a**, **26b** (0.26 g, 86%). Proportion of the two isomers were determined by ¹H nmr and are **26a** (78%) and **26b** (22%), mp 66°; ¹H nmr (deuteriochloroform): δ 4.04 (s, 3H, OCH₃^a), 4.08 (s, 3H, OCH₃^b), 4.20 (s, 1H, OH^{a+b}), 5.86 (s, 1H, CH^a), 6.80 (s, 1H, CH^b), 7.19 (s, 1H, H₅^a), 7.30 (m, 5H, Ph), 7.53 (m, 3H, Ph), 7.81 (m, 1H, Ph), 8.06 (m, 1H, Ph), 8.51 (s, 1H, H₄^b).

Anal. Calcd. for C₁₈H₁₆O₄N₂S: C, 60.77; H, 4.49; N, 7.90. Found: C, 60.6; H, 4.8; N, 7.6.

6-Methoxy-4-methyl-3-phenylsulfonylpyridazine (**27a**), 6-Methoxy-5-methyl-3-phenyl sulfonylpyridazine (**27b**) and 4,5-Dimethyl-6-methoxy-3-phenylsulfonylpyridazine (**27c**).

Metalation of **24** (0.21 g, 0.86 mmole) according to the general procedure with *n*-butyllithium 2.5 M (0.75 ml, 1.85 mmoles) and 2,2,6,6-tetramethylpiperidine (0.32 ml, 1.85 mmoles), t₁ = 35 minutes then reaction with methyl iodide (0.12 ml, 1.85 mmoles), t₂ = 60 minutes gave after purification by column chromatography on silica gel with a mixture of dichloromethane/ethyl acetate (9:1) as an eluent, following by hplc (50 μl, λ = 230 nm) with a mixture of methanol/water (6:4) as an eluent a yellow oil of three metalation isomers **27a**, **27b**, **27c** (0.10 g, 61%). Proportion of the three metalation isomers were determined by ¹H nmr and are **27a** (55%), **27b** (15%) and **27c** (30%); ¹H nmr (deuteriochloroform): δ 2.33 (s, 3H, CH₃^{b+c}), 2.79 (s, 3H, CH₃^{a+c}), 4.11 (s, 3H, OCH₃^a), 4.19 (s, 3H, OCH₃^b), 4.30 (s, 3H, OCH₃^c), 6.84 (s, 1H, H₅^a), 7.30 (s, 1H, H₄^b), 7.66 (m, 3H, Ph), 8.08 (m, 2H, Ph).

Anal. Calcd. for C₁₂H₁₂N₂O₃S: C, 54.54; H, 4.54; N, 10.60. Found C, 54.2; H, 4.5; N, 10.9.

3-[(2-Hydroxypropyl)sulfonyl]-6-methoxy-pyridazine (**29**).

Metalation of **28** (0.10 g, 0.53 mmole) according to the general procedure with *n*-butyllithium 2.5 M (0.47 ml, 1.17 mmoles) and diisopropylamine (0.17 ml, 1.17 mmoles), t₁ = 30 minutes then reaction with acetaldehyde (1 ml, 18 mmoles), t₂ = 30 minutes gave after purification by column chromatography on silica gel with ethyl acetate as an eluent a yellow powder of **29** (0.07 g, 60%), mp 125-127°; ¹H nmr (deuteriochloroform): δ 1.33 (d, 3H, J_{CH₃-CH} = 6.4 Hz, CH₃), 3.36 (s, 1H, OH), 3.69 (m, 2H, CH₂), 4.23 (s, 3H, OCH₃), 4.47 (m, 1H, CH), 7.20 (d, 1H, J₄₋₅ = 9.2 Hz, H₅), 8.06 (d, 1H, J₄₋₅ = 9.2 Hz, H₄)

Anal. Calcd. for C₈H₁₂N₂O₄S: C, 41.42; H, 5.21; N, 12.07. Found: C, 41.6; H, 5.0; N, 11.8.

4-[(1-Hydroxy)ethyl]-3-[(2-hydroxypropyl)sulfonyl]-6-methoxy pyridazine (**30**).

Metalation of **28** (0.10 g, 0.53 mmole) according to the general procedure with *n*-butyllithium 2.5 *M* (0.47 ml, 1.17 mmoles) and 2,2,6,6-tetramethylpiperidine (0.20 ml, 1.17 mmoles), $t_1 = 30$ minutes then reaction with acetaldehyde (1 ml, 18 mmoles), $t_2 = 30$ minutes gave after purification by column chromatography on silica gel with a mixture of ethanol/ethyl acetate (1:9) as an eluent an orange oil of two metalation products **29**, **30** (0.08 g, 62%). Proportion of the two metalation products were determined by ^1H nmr and are **29** (70%) and **30** (30%); ^1H nmr (deuteriochloroform): δ 1.28 (d, 3H, $J_{\text{CH}_3\text{-CH}} = 6.4$ Hz, CH_3^{30}), 1.33 (d, 3H, $J_{\text{CH}_3\text{-CH}} = 6.4$ Hz, CH_3^{29}), 1.50 (d, 3H, $J_{\text{CH}_3\text{-CH}} = 6.2$ Hz, CH_3^{30}), 3.62-3.89 (m, (2+1)H, $\text{CH}_2^{29+30} + \text{OH}^{29+30}$), 4.16 (s, 3H, OCH_3^{30}), 4.19 (s, 3H, OCH_3^{29}), 4.44 (m, (1+1)H, $\text{CH}^{(29+30)}$), 5.60 (q, 1H, $J_{\text{CH-CH}_3} = 6.2$ Hz, CH^{30}), 7.18 (d, 1H, $J_{4-5} = 9.2$ Hz, H_5^{29}), 7.42 (s, 1H, H_5^{30}), 8.03 (d, 1H, $J_{4-5} = 9.2$ Hz, H_4^{29}).

3-(Deuteriomethylsulfonyl)-6-methoxy pyridazine (**31a**), 3-(Deuteriomethylsulfonyl)-4-deuterio-6-methoxy pyridazine (**31b**) and 3-(Deuteriomethylsulfonyl)-5-deuterio-6-methoxy pyridazine (**31c**).

Metalation of **28** (0.15 g, 7.98 mmoles) according to the general procedure with *n*-butyllithium 2.5 *M* (0.70 ml, 1.75 mmoles) and diisopropylamine (0.25 ml, 1.75 mmoles), $t_1 = 30$ minutes then reaction with ethyl alcohol-*d* (1 ml), $t_2 = 25$ minutes following by chloride deuteride (0.5 ml), $t_2 = 5$ minutes gave after purification by column chromatography on silica gel with a mixture of dichloromethane/ethyl acetate (8:2) as an eluent a yellow oil of three metalation products **31a**, **31b**, **31c** (0.09 g, 57%). Proportion of the three metalation products were determined by ^1H nmr and are **31a** (40%), **31b** (37%), **31c** (23%); ^1H nmr: δ 3.34 (m, 2H,

CH_2D), 4.20 (s, 3H, OCH_3), 7.17 (d, 1H, $J_{4-5} = 9.2$ Hz, H_5^a), 7.17 (s, 1H, H_5^b), 8.01 (d, 1H, $J_{4-5} = 9.2$ Hz, H_4^a), 8.02 (s, 1H, H_4^c).

REFERENCES AND NOTES

- [1] L. Horner, A. J. Lawson, and G. Simons, *Phosphorus Sulfur*, **12**, 779 (1983).
- [2] N. Furukawa, F. Takahashi, T. Kawai, K. Kishimoto, S. Ogawa, and S. Oae, *Phosphorus Sulfur*, **16**, 167 (1983).
- [3] M. Iwao, T. Iihama, M. M. Mahalanabis, H. Perrier, and V. Snieckus, *J. Org. Chem.*, **54**, 24 (1989).
- [4] J. N. Bonfiglio, *J. Org. Chem.*, **51**, 2833 (1986).
- [5] J. G. Lombardino, *J. Org. Chem.*, **36**, 1843 (1971).
- [6] H. Watanabe, R. Scharwartz, C. R. Hauser, J. Lewis, and D. W. Slocum, *Can. J. Chem.*, **47**, 1543 (1969).
- [7] G. Quéguiner, F. Marsais, V. Snieckus, and J. Epszajn, *Adv. Heterocyclic Chem.*, Vol **52**, Academic Press, Inc., 1991, p 187.
- [8] C. Quesnelle, T. Iihama, T. Aubert, H. Perrier, and V. Snieckus, *Tetrahedron*, **41**, 861 (1985).
- [9] J. S. Ward and L. Merritt, *J. Heterocyclic Chem.*, **28**, 765 (1991).
- [10] H. Tanaka, H. Hayakawa, S. Iijima, K. Haragushi, and T. Miyasaka, *Tetrahedron*, **41**, 861 (1985).
- [11] A. Turck, N. Plé, G. Queguiner, *Heterocycles*, **37**, 2149 (1994).
- [12] J. H. M. Hill and J. G. Krause, *J. Org. Chem.*, **29**, 1642 (1964).
- [13] G. B. Barlin and W. V. Brown, *J. Chem. Soc. C*, 921 (1969).
- [14] B. M. Trost and D. P. Curran, *Tetrahedron Letters*, **22**, 1287 (1981).
- [15] M. Madesclaire, *Tetrahedron*, **20**, 5459 (1986).
- [16] N. Furukawa, T. Shibutani, K. Matsumura, and H. Fujihara, *Tetrahedron Letters*, **27**, 3899 (1986).
- [17] T. Shibutani, H. Fujihara, and N. Furukawa, *Tetrahedron Letters*, **32**, 2943 (1991).
- [18] All experiments have been performed at -75° in tetrahydrofuran as the solvent.