Tetrahedron Vol 49, No 3, pp 599-606, 1993
Printed in Great Britain

0040-4020/93 $5 00+ 00
Pergamon Press Ltd

ON THE METALATION OF 3-SUBSTITUTED AND 3,6-DISUBSTITUTED PYRIDAZINES

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(*Received in Germany* 21 *September* 1992)

Key Words metalation, pyridazines, lithiation

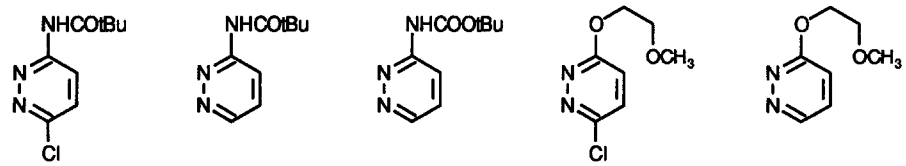
Abstract: Starting from 3,6-dichloropyridazine, a series of new pyridazines bearing lithiation-directing groups in α-position to a ring nitrogen atom (compounds **1-5**) was prepared Metalation employing lithium alkylamides was found to afford *ortho*-substituted pyridazines The regioselectivity, depending on the nature of the metalating agent, is discussed

INTRODUCTION

Pyridazine derivatives continue to attract considerable interest, as reflected by recent reviews regarding chemical and biological properties [1,2] The recent discovery[3] of a natural product containing this heteroarene system (*Pyridazomycin*) most probably will stimulate even broader interest in 1,2-diazine chemistry

The main difficulty encountered on attempted introduction of a functionalised carbon side-chain into the pyridazine nucleus results from its pronounced electron deficiency C-C bond formation by electrophilic aromatic substitution thus is not a suitable methodology Homolytic substitution reactions of the protonated pyridazine nucleus, employing nucleophilic carbon-centered radicals, however, have been shown to close this gap in many cases (alkylation, acylation, alkoxycarbonylation, formylation) [4] More recently, the first examples of the utilisation of *ortho*-directed metalation for the functionalisation of this ring system have been reported [5] 3,6-Dichloropyridazine, 3-chloro-6-methoxypyridazine and 3,6-dimethoxypyridazine were employed as educts in these studies

In extension of these investigations, we here report on the synthesis of a series of so far unknown pyridazines bearing lithiation-directing groups in α-position to a ring nitrogen atom (namely the pivalamides **1**, **2**, the urethane **3** as well as the methoxyethoxy compounds **4**, **5**) and on their behaviour in metalation experiments



1 **2** **3** **4** **5**

RESULTS AND DISCUSSION

Synthesis of selected 3-substituted and 3,6-disubstituted 1,2-diazine derivatives as metalation educts:

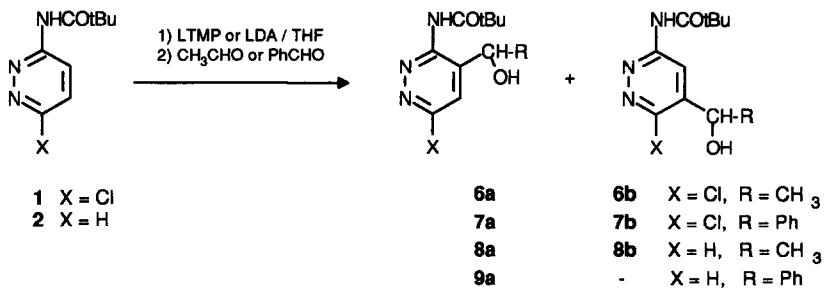
For the synthesis of compounds **1-3**, commercially available 3,6-dichloropyridazine was transformed in 80% yield into 6-amino-3-chloropyridazine following a known procedure [6] Reductive dehalogenation of this product turned out to be advantageous for the preparation of 3-aminopyridazine (85%) as compared with the previously reported approach[7] (ammonolysis of 3-bromopyridazine, 44% yield) Both aminopyridazines thus prepared were treated with pivaloyl chloride/triethylamine in tetrahydrofuran solution to give the sterically hindered amides **1** and **2** in satisfactory yields The *tert*-butyl carbamate **3** could be prepared in 78% yield by heating 3-aminopyridazine with BOC-anhydride in the absence of a solvent and subsequent purification by column chromatography For the preparation of the methoxyethoxypyridazine **4**, 3,6-dichloropyridazine was treated with sodium 2-methoxyethoxide in dry tetrahydrofuran at room temperature Compound **4** thus obtained in 88% yield then could be smoothly dechlorinated by catalytic hydrogenation (Pd/C, sodium hydroxide, ethanol as solvent) to give the ether **5** in 77% overall yield

Metalation experiments:

a) Metalation of compounds 1-3

The results of metalation experiments employing lithium 2,2,6,6-tetramethylpiperidide (LTMP) or lithium diisopropylamide (LDA) as metalating agents, together with the products obtained after quenching with acetaldehyde or benzaldehyde are collected in Scheme 1 and Table 1

Scheme 1



1 X = Cl
2 X = H

6a **6b** X = Cl, R = CH_3
7a **7b** X = Cl, R = Ph
8a **8b** X = H, R = CH_3
9a - X = H, R = Ph

3

10a R = CH_3
11a R = Ph

Table 1 Metalation of **1-3**

Entry	Educt	Metalating agent	Equivalents reagent	Conditions[a]	Electrophile	Products (% yield)		Total yield (%)
1	**1**	LTMP	2 2	A	CH_3CHO	**6a** (0)	**6b** (0)	0
2	**1**	LTMP	3 2	A	CH_3CHO	**6a** (14)	**6b** (41)	55
3	**1**	LTMP	4 0	A	CH_3CHO	**6a** (35)	**6b** (65)	100
4	**1**	LTMP	4 0	A	PhCHO	**7a** (28)	**7b** (55)	83
5	**1**	LDA	4 0	A	CH_3CHO	**6a** (0)	**6b** (82)	82
6	**1**	LDA	4 0	A	PhCHO	**7a** (0)	**7b** (57)	57
7	**1**	LDA	4 0	B	PhCHO	**7a** (0)	**7b** (68)	68
8	**2**	LTMP	4 0	C	CH_3CHO	**8a** (0)	**8b** (0)	0
9	**2**	LTMP	4 0	A	CH_3CHO	**8a** (52)	**8b** (4)	56
10	**2**	LTMP	4 0	A	PhCHO	**9a** (62)	-	62
11	**3**	LTMP	4 0	A	CH_3CHO	**10a** (37)	-	37
12	**3**	LTMP	4 0	A	PhCHO	**11a** (36)	-	36

[a] Conditions A metalation -70°C, 1 5 h, reaction with electrophile -70°C, 1 5 h
B metalation -70°C, 3 0 h, reaction with electrophile -70°C, 2 0 h
C metalation 0°C, 45 min, reaction with electrophile 0°C, 1 5 h

Initial experiments with N-(6-chloro-3-pyridazinyl)pivalamide (**1**) indicated that employment of the theoretically required two equivalents of metalating agent (LTMP), followed by addition of acetaldehyde only leads to the recovery of unchanged starting material in almost quantitative yield The use of 3 2 equivalents of LTMP resulted in a 55% total yield of reaction products (compounds **6a,b**). Quantitative lithiation can be achieved by employing 4 equivalents of LTMP Accordingly, in all the following experiments with compounds **1-3**, this large excess of lithium dialkylamide was used in order to gain maximal conversions

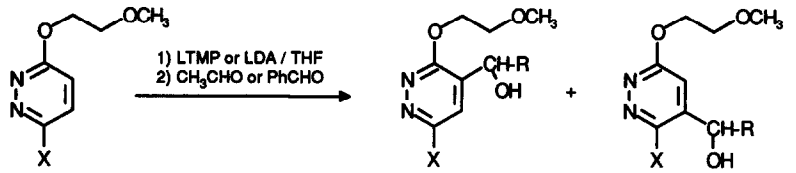
Interestingly, the major component in the mixtures obtained after lithiation of **1** with LTMP and subsequent reaction with acetaldehyde or benzaldehyde (entries 3 and 4) results from lithiation *ortho* to the chlorine substituent (compounds **6b**, **7b**) Application of LDA (entries 5-7) was found to permit exclusive functionalisation of the pyridazine nucleus *ortho* to the chlorine atom

On the other hand, introduction of a carbon side-chain exclusively *ortho* to the (protected) amino function may well be achieved if there is no competing directing group present (entries 9-12) Thus, N-(3-pyridazinyl)pivalamide (**2**) as well as *tert*-butyl N-(3-pyridazinyl)carbamate (**3**) on action of LTMP undergoes regioselective lithiation at C-4 to give compounds **8a**, **9a**, **10a**, **11a**, albeit in only moderate yields Only in the case of **2**, a small amount of a reaction product (**8b**) resulting from lithiation at C-5 (*meta* to the amide function) could be detected It should be noted that in the case of the carbamate **3**, the initially formed alcohols are subject to intramolecular transesterification during work-up to afford the pyridazine-annelated 1,3-oxazine derivatives **10a**, **11a**

b) Metalation of compounds 4 and 5

Similar to the observations discussed above, also in the series of the (methoxyethoxy)pyridazines **4** and **5**, the twofold theoretical minimum amount of the metalating agent (i e 2 2 equivalents) is required to achieve lithiation of the pyridazine nucleus The results obtained in these experiments are displayed in Scheme 2 and Table 2

Scheme 2



4 X = Cl
5 X = H

12a **12b** X = Cl, R = CH_3
13a **13b** X = Cl, R = Ph
14a - X = H, R = CH_3
15a - X = H, R = Ph

Table 2. Metalation of **4** and **5**

Entry	Educt	Metalating agent	Equivalents reagent	Conditions[a]	Electrophile	Products (% yield)		Total yield (%)
1	**4**	LTMP	1 2	A	CH_3CHO	**12a** (0)	**12b** (0)	0
2	**4**	LTMP	2 2	A	CH_3CHO	**12a** (53)	**12b** (36)	89
3	**4**	LTMP	2 2	B	CH_3CHO	**12a** (31)	**12b** (31)	62
4	**4**	LTMP	2 2	A	PhCHO	**13a** (48)	**13b** (32)	80
5	**4**	LDA	2 2	A	CH_3CHO	**12a** (33)	**12b** (49)	82
6	**4**	LDA	2 2	A	PhCHO	**13a** (28)	**13b** (55)	83
7	**5**	LTMP	2 2	A	CH_3CHO	**14a** (12)	-	12
8	**5**	LTMP	2 2	A	PhCHO	**15a** (15)	-	15
9	**5**	LTMP	4 0	A	PhCHO	**15a** (26)	-	26

[a] Conditions A. metalation -70°C, 1 5 h, reaction with electrophile -70°C, 1 5 h
B metalation -70°C, 2 5 h, reaction with electrophile -70°C, 1 5 h

Whereas in the case of 3-(2-methoxyethoxy)pyridazine **5** lithiation with LTMP occurs exclusively in position 4 to give compounds **14a** and **15a** (in low yields), the situation was found to be more complex with the chloro-substituted congener **4** Here, mixtures of regioisomeric carbinols (compounds **12a,b**, **13a,b**) are formed in high yields Depending on the lithiating agent employed, the ratio of products can be shifted with LTMP, preferential formation of compounds **12a** and **13a** (bearing the carbon side-chain *ortho* to the ether function) is observed, the use of LDA favours lithiation *ortho* to the chlorine atom, thus leading predominantly to the isomeric compounds **12b** and **13b**

CONCLUSION

The metalation experiments carried out clearly indicate that with pyridazine derivatives **1-5**, metalation of the pyridazine nucleus only can be achieved by employing a significant excess of the lithium dialkylamide This phenomenon could be explained in terms of competitive complexation processes, which at present is the subject of further (spectroscopic and theoretical) investigations

From the preparative point of view, the *ortho*-directed lithiation of the 3-acylaminopyridazine **2** appears to be a suitable method for the synthesis of 3-aminopyridazines bearing a functionalised carbon side chain in *ortho* position Vicinally disubstituted compounds of this type are of particular interest as potential precursors for fused pyridazines On the other hand, 3-aminopyridazine derivatives with the carbon substituent in *meta* position to the amino function can be easily obtained when an additional chlorine atom (at the second α-position) is present in the educt, as demonstrated by the experiments employing compound **1**

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage microscope and are uncorrected Infrared spectra were taken on a Jasco IRA-1 and on a Beckman 4250 spectrometer (KBr pellets) ^{1}H NMR spectra were recorded on a Bruker AC 80 (80 MHz), on a Varian EM 360 L (60 MHz), or on a Bruker 200 MHz spectrometer with TMS as internal reference Column chromatography was carried out on Merck silica gel 60, 0 063-0 200 mm (70-230 mesh ASTM) Microanalyses were performed at the Institute of Physical Chemistry, University of Vienna, and by the INSA analytical service All metalations were carried out under an argon atmosphere All reagents were freshly distilled, THF was dried with a benzophenone-sodium mixture and distilled just before use

3-Aminopyridazine[7]
A mixture of 6-amino-3-chloropyridazine[6] (1.29 g, 10 mmol), sodium hydroxide (440 mg, 11 mmol), and 10% Pd/C catalyst (150 mg) was hydrogenated at atmospheric pressure for 1 5 h The catalyst was filtered off and the solution was evaporated *in vacuo* The residue was repeatedly extracted with boiling acetone to afford, after removal of the solvent, pale yellow crystals (809 mg, 85%), mp 168-169°C (ref [7] 169-170°C)

N-(6-Chloro-3-pyridazinyl)pivalamide (1)
To an ice-cooled suspension of 6-amino-3-chloropyridazine[6] (800 mg, 6 18 mmol) and triethylamine (1 01 g, 10 mmol) in dry tetrahydrofuran (70 ml) was added dropwise a solution of pivaloyl chloride (1 94 g, 16 1 mmol) in dry tetrahydrofuran (10 ml). The mixture was stirred at room temperature for 4 h, then the solvent was removed *in vacuo* The residue was taken up in dichloromethane and washed with 0 2 N aqueous sodium hydroxide and water The organic layer was dried (sodium sulfate) and evaporated. Purification of the residue by column chromatography (eluting with dichloromethane-ethyl acetate, 4 1), followed by recrystallisation from ethyl acetate-light petroleum afforded colourless crystals (805 mg, 61%), mp 159°C - IR 3360, 2960, 1670, 1560, 1480 cm^{-1} - ^{1}H NMR (80 MHz, $CDCl_3$) δ 8 52 (d, J = 9 3 Hz, 1 H, H-4), 8 46 (br s, 1 H, NH), 7 49 (d, J = 9 3 Hz, 1 H, H-5), 1 35 (s, 9 H, CH_3) - Anal calcd for $C_9H_{12}ClN_3O$ C, 50 59, H, 5 66, N, 19 67 Found C, 50 78, H, 5 44, N, 19 44

N-(3-Pyridazinyl)pivalamide (2)
Preparation as described for compound **1**, starting from 3-aminopyridazine[7] (1 00 g, 10 53 mmol), triethylamine (1 52 g, 15 mmol), and pivaloyl chloride (1 81 g, 15 mmol) Column chromatography (eluting with ethyl acetate) and subsequent recrystallisation from ethyl acetate-light petroleum gave colourless crystals (1 23 g, 65%), mp 126°C - IR 3180, 2960, 1670, 1570, 1500 cm^{-1} - ^{1}H NMR (80 MHz, $CDCl_3$) δ 8 93 (dd, J_{4-6} = 1 4 Hz, J_{5-6} = 6 0 Hz, 1 H, H-6), 8 79 (br s, 1 H, NH), 8.49 (dd, J_{4-5} = 8 9 Hz, J_{4-6} = 1 4 Hz, 1 H, H-4), 7 48 (dd, J_{4-5} = 8 9 Hz, J_{5-6} = 6 0 Hz, 1 H, H-5), 1 36 (s, 9 H, CH_3) - Anal calcd for $C_9H_{13}N_3O$ C, 60 31, H, 7 31, N, 23 44 Found C, 60 55, H, 7 17, N, 23 48

tert-Butyl N-(3-pyridazinyl)carbamate (3)
A mixture of 3-aminopyridazine[7] (450 mg, 4 74 mmol) and di-*tert*-butyl pyrocarbonate (1 54 g, 7 05 mmol) was fused together by gentle heating, then it was dissolved in dry dichloromethane (20 ml) To the stirred solution, a mixture of dry pyridine (10 ml) and dry dichloromethane (10 ml) was added dropwise, and stirring was continued for 3 h After dilution with dichloromethane, the solution was washed with 0 1 N hydrochloric acid and water, then it was dried (sodium sulfate) and evaporated *in vacuo* The residue was purified by column chromatography (eluting with ethyl acetate), followed by recrystallisation from light petroleum to afford pale yellow crystals (722 mg, 78%), mp 109-110°C - IR 3180, 2970, 1710, 1580, 1510 cm^{-1} - ^{1}H NMR (80 MHz, $CDCl_3$) δ 8 86 (dd, J_{4-6} = 1 4 Hz, J_{5-6} = 6 1 Hz, 1 H, H-6), 8 24 (dd, J_{4-5} = 9 0 Hz, J_{4-6} = 1 4 Hz, 1 H, H-4), 8 17 (br s, 1 H, NH), 7 42 (dd, J_{4-5} = 9 0 Hz, J_{5-6} = 6 1 Hz, 1 H, H-5), 1 54 (s, 9 H, CH_3) - Anal calcd for $C_9H_{13}N_3O_2$ C, 55 37, H, 6 71, N, 21 52 Found C, 55 63, H, 6.49, N, 21 41.

3-Chloro-6-(2-methoxyethoxy)pyridazine (4)
To a stirred solution of sodium 2-methoxyethoxide, prepared from 2-methoxyethanol (2.28 g, 30 mmol) and metallic sodium (690 mg, 30 mmol), in dry tetrahydrofuran (100 ml) was added 3,6-dichloropyridazine (3 00 g, 20 14 mmol) The solution, which was kept under an argon atmosphere, was stirred at room temperature for 30 min Water (50 ml) was added, then the mixture was concentrated *in vacuo* to a volume of about 50 ml and it was exhaustively extracted with dichloromethane The combined extracts were washed with water, dried

(sodium sulfate), and evaporated *in vacuo*. Recrystallisation of the residue from light petroleum gave colourless crystals (3 34 g, 88%), mp 40-41°C - IR· 3050, 2860, 1570 cm^{-1} - ^1H NMR (80 MHz, $CDCl_3$) δ 7 32, 6 95 (each d, J = 9 1 Hz, 2 H, H-4, H-5), 4 70-4 50 (m, 2 H, CH_2), 3 80-3.65 (m, 2 H, CH_2), 3 37 (s, 3 H, CH_3) - Anal calcd for $C_7H_9ClN_2O_2$· C, 44 58; H, 4 81, N, 14 85 Found C, 44 89, H, 4 64, N, 14 84

3-(2-Methoxyethoxy)pyridazine (5)

To a solution of compound 4 (188 mg, 1 mmol) in absolute ethanol (10 ml) was added sodium hydroxide (60 mg, 1 5 mmol) and 10% Pd/C catalyst, then the mixture was hydrogenated at atmospheric pressure for 2 h The catalyst was filtered off, the solvent was removed *in vacuo*, and the residue was taken up in dichloromethane This solution was washed with water, dried (sodium sulfate), and evaporated *in vacuo*. Kugelrohr distillation (80°C, 80 mbar) of the residue afforded a colourless liquid (136 mg, 88%) - IR 2960, 1605 cm^{-1}. ^1H NMR (80 MHz, $CDCl_3$) δ 8 84 (dd, J_{4-6} = 1 2 Hz, J_{5-6} = 5 5 Hz, 1 H, H-6), 7 41 (dd, J_{4-5} = 9 0 Hz, J_{5-6} = 5 5 Hz, 1 H, H-5), 7 04 (dd, J_{4-5} = 9 0 Hz, J_{4-6} = 1 2 Hz, 1 H, H-4), 4 80-4 60 (m, 2 H, CH_2), 3 90-3.70 (m, 2 H, CH_2), 3 45 (s, 3 H, CH_3) - Anal calcd for $C_7H_{10}N_2O_2$ C, 54 54, H, 6 54, N, 18 17 Found C, 54 76, H, 6 60, N, 18 49

General procedure for metalation of compounds 1-5.

A solution of *n*-BuLi in hexane (nx mmol) was added at -30°C to stirred anhydrous tetrahydrofuran (25 ml) under argon. The chosen alkylamine (diisopropylamine or 2,2,6,6-tetramethylpiperidine, nx mmol) was added, the mixture was allowed to warm to 0°C (15 min) and was kept at 0°C for 0 5 h The solution was then cooled to -70°C The pyridazine to metalate (x mmol) was dissolved in tetrahydrofuran (5 ml) under argon and the solution was slowly added (5 min) to the metalation mixture. The metalation reaction was performed during 1 5 h at -70°C (unless otherwise stated, see Tables), then the electrophile (acetaldehyde. 1 ml; benzaldehyde 1 2 nx mmol) was added slowly (5 min) The reaction was performed during 1 5 h at -70°C (unless otherwise stated, see Tables) The solution was then slowly hydrolysed at -70°C with a mixture of 2 N aqueous hydrochloric acid (2 ml), ethanol (4 ml), and tetrahydrofuran (4 ml) and warmed to 0°C A saturated solution of sodium hydrogencarbonate was added until neutralisation and the mixture was evaporated *in vacuo* to give an aqueous residue This residue was extracted with dichloromethane (4 x 25 ml) The combined extracts were dried over magnesium sulfate and evaporated to dryness to afford a crude product which was purified by column chromatography on silica gel

N-[6-Chloro-4-(1-hydroxyethyl)-3-pyridazinyl]pivalamide (6a)
N-[6-Chloro-5-(1-hydroxyethyl)-3-pyridazinyl]pivalamide (6b)

Table 1, Entry 3

General procedure with **1** (151 mg, 0 71 mmol), 1 6 M *n*-BuLi in hexane (1 78 ml, 2 85 mmol), TMP (0 48 ml, 2 85 mmol) The eluent was a 2 3 mixture of ethyl acetate and dichloromethane Compound **6a** was obtained as a colourless solid (120 mg, 65%), mp 160°C - ^1H NMR (200 MHz, $CDCl_3$) δ 9 27 (br s, 1 H, NH), 7 59 (s, 1 H, H-5), 4 92 (q, J = 6 Hz, 1 H, CH), 4 70 (br s, 1 H, OH), 1 47 (d, J = 6 Hz, 3 H, CH_3), 1 37 (s, 9 H, *tert*-Bu) - Anal calcd for $C_{11}H_{16}ClN_3O_2$ C, 51 26, H, 6 21, N, 16 31 Found C, 51 1, H, 6 2, N, 15.9 Compound **6b** was obtained as a colourless solid (64 mg, 35%), mp 120°C - ^1H NMR (60 MHz, $CDCl_3$) δ 8 98 (br s, 1 H, NH), 8 74 (s, 1 H, H-4), 5 3 (q, J = 6 Hz, 1 H, CH), 3.3 (br s, 1 H, OH), 1 55 (d, J = 6 Hz, 3 H, CH_3), 1 35 (s, 9 H, *tert*-Bu) - Anal calcd for $C_{11}H_{16}ClN_3O_2$ C, 51 26, H, 6 21, N, 16 31 Found C, 51 2, H, 6 2, N, 15 9

N-[6-Chloro-4-(hydroxy)(phenyl)methyl-3-pyridazinyl]pivalamide (7a)
N-[6-Chloro-5-(hydroxy)(phenyl)methyl-3-pyridazinyl]pivalamide (7b)

Table 1, Entry 4

General procedure with **1** (150 mg, 0 70 mmol), 1 6 M *n*-BuLi in hexane (1 78 ml, 2 85 mmol), TMP (0 48 ml, 2 85 mmol), benzaldehyde (0 30 ml, 2 95 mmol) The eluent was a 1 9 mixture of ethyl acetate and dichloromethane Compound **7a** was obtained as a pale yellow solid (63 mg, 28%), mp 77°C - ^1H NMR (60 MHz, $CDCl_3$) δ 9 0 (br s, 1 H, NH), 7 55 (s, 1 H, H-5), 7 30 (m, 5 H, Ph), 5 95 (s, 1 H, CH), 5 35 (br s, 1 H, OH), 1 2 (s, 9 H, *tert*-Bu) - Anal calcd for $C_{16}H_{18}ClN_3O_2$ C, 60 09, H, 5 63, N, 13 14 Found C, 60 5, H, 5 6, N, 12 8 An amount of 24 mg (16%) of starting material **1** was recovered

Compound **7b** was obtained as a colourless solid (124 mg, 55%), mp 77°C - ^{1}H NMR (200 MHz, $CDCl_3$) δ 8 93 (s, 1H, H-4), 8 67 (br s, 1 H, NH), 7 33 (m, 5 H, Ph), 5.95 (s, 1 H, CH), 3.91 (br s, 1 H, OH), 1.32 (s, 9 H, *tert*-Bu) - Anal. calcd for $C_{16}H_{18}ClN_3O_2$ C, 60 09, H, 5 63, N, 13 14. Found C, 60 3; H, 5.6; N, 12.9.

N-[4-(1-hydroxyethyl)-3-pyridazinyl]pivalamide (**8a**)

Table 1, Entry 9

General procedure with **2** (146 mg, 0 81 mmol), 2 5 M *n*-BuLi in hexane (1.30 ml, 3 25 mmol), TMP (0 60 ml, 3 56 mmol) The eluent was a 1 1 mixture of ethyl acetate and dichloromethane Compound **8a** was obtained as a colourless solid (94 mg, 52%), mp 138°C - ^{1}H NMR (60 MHz, $CDCl_3$) δ 9 85 (br s, 1 H, NH), 8 85 (d, $J_{5\text{-}6}$ = 5.5 Hz, 1 H, H-6), 7 52 (d, $J_{5\text{-}6}$ = 5 5 Hz, 1 H, H-5), 5 3 (br s, 1 H, OH), 4 98 (q, J = 6 Hz, 1 H, CH), 1 45 (d, J = 6 Hz, 1 H, CH_3), 1 3 (s, 9 H, *tert*-Bu) - Anal calcd for $C_{11}H_{17}N_3O_2$ C, 59.14; H, 7.62, N, 18 82 Found C, 59 3, H, 7.7, N, 18 6.

A small amount of **8b** (7 2 mg, 4%) was isolated and characterised by ^{1}H NMR (60 MHz, $CDCl_3$) δ 9 00 (s, 1 H, H-6), 8 6 (br s, 1 H, NH), 8 45 (s, 1 H, H-4), 4 95 (q, J = 7 Hz, 1 H, CH), 3 45 (br s, 1 H, OH), 1 55 (d, J = 7 Hz, 3 H, CH_3), 1 35 (s, 9 H, *tert*-Bu).

N-[4-(hydroxy)(phenyl)methyl-3-pyridazinyl]pivalamide (**9a**)

Table 1, Entry 10

General procedure with **2**, same quantities and eluent as for **8a**, except that benzaldehyde (0.30 ml, 2.95 mmol) was used as electrophile. Compound **9a** was obtained as a pale yellow solid (144 mg, 62%), mp 66°C - ^{1}H NMR (60 MHz, $CDCl_3$) δ 9 2 (br s, 1 H, NH), 8 9 (d, $J_{5\text{-}6}$ = 6 Hz, 1 H, H-6), 7 45 (d, $J_{5\text{-}6}$ = 6 Hz, 1 H, H-5), 7 3 (m, 5 H, Ph), 5 95 (s, 1 H, CH), 5 5 (br s, 1 H, OH), 1 25 (s, 9 H, *tert*-Bu) - Anal calcd for $C_{16}H_{19}N_3O_2$ C, 67 37, H, 6 67, N, 14 74 Found C, 67 4, H, 7 1, N, 14 8

5,8-Dihydro-5-methyl-7*H*-pyridazino[3,4-*d*][1,3]oxazin-7-one (**10a**)

Table 1, Entry 11

General procedure with **3** (155 mg, 0 79 mmol), 1 6 M *n*-BuLi in hexane (2 00 ml, 3 20 mmol), TMP (0.54 ml, 3 20 mmol) The eluent was ethyl acetate Two products were obtained (80 mg) which were **10a** and a product still bearing the *tert*-butyloxycarbonyl group Both products were dissolved in water (5 ml), acidified to pH 1 and stirred overnight After neutralisation with a saturated aqueous solution of sodium hydrogencarbonate, the mixture was extracted with ethyl acetate. Compound **10a** was obtained as a colourless solid (48 mg, 37%), mp 219°C (dec) - ^{1}H NMR (60 MHz, DMSO-d_6) δ 8 85 (d, $J_{3\text{-}4}$ = 5 5 Hz, 1 H, H-3), 7 45 (d, $J_{3\text{-}4}$ = 5 5 Hz, 1 H, H-4), 5 55 (m, 1 H, H-5), 3 3 (br s, 1 H, NH), 1 6 (d, J = 6 Hz, 3 H, CH_3) - Anal. calcd for $C_7H_7N_3O_2$ C, 50 90, H, 4 24, N, 25 45 Found C, 51 1, H, 4 3, N, 25 1

5,8-Dihydro-5-phenyl-7*H*-pyridazino[3,4-*d*][1,3]oxazin-7-one (**11a**)

Table 1, Entry 12

General procedure with **3** (162 mg, 0 83 mmol), 1 6 M *n*-BuLi in hexane (2 00 ml; 3 20 mmol), TMP (0 57 ml, 3 38 mmoles) Hydrolysis was performed at -70°C with water (10 ml), then the mixture was warmed to room temperature It was evaporated and the aqueous residue was extracted with dichloromethane The aqueous phase was neutralised with 2 N aqueous hydrochloric acid and **11a** was obtained as a pale yellow precipitate (68 mg, 36%), mp 248°C (dec) - ^{1}H NMR (60 MHz, DMSO-d_6) δ 8 8 (d, $J_{3\text{-}4}$ = 5.5 Hz, 1 H, H-3), 7 35 (br s, 5 H, Ph), 7 05 (d, $J_{3\text{-}4}$ = 5 5 Hz, 1 H, H-4), 6 5 (s, 1 H, H-5), 3 25 (br s, 1 H, NH). - Anal calcd for $C_{12}H_9N_3O_2$ C, 63 44, H, 3 96, N, 18 50 Found C, 63 5, H, 4 0, N, 18 6

3-Chloro-5-(1-hydroxyethyl)-6-(2-methoxyethoxy)pyridazine (**12a**)
3-Chloro-4-(1-hydroxyethyl)-6-(2-methoxyethoxy)pyridazine (**12b**)

Table 2, Entry 2

General procedure with **4** (150 mg; 0 80 mmol), 1 6 M *n*-BuLi in hexane (1 10 ml, 1.76 mmol), TMP (0 30 ml, 1 78 mmol) The eluent was a 1 · 9 mixture of ethyl acetate and dichloromethane. A mixture of **12a** and **12b** was obtained as a yellow oil (165 mg, 89 %) - **12a** ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.57 (s, 1 H, H-4), 5 02 (q, J = 6 Hz, 1 H, CH), 4 65-4 50 (m, 2 H, CH_2), 4 20 (br s, 1 H, OH), 3.80-3 65 (m, 2 H, CH_2), 3.35 (s, 3 H, OCH_3), 1 45 (d, J = 6 Hz, 3 H, CH_3) - **12b** ^{1}H NMR (200 MHz, $CDCl_3$) δ 7 35 (s, 1 H, H-5), 5.02 (q,

J = 6 Hz, 1 H, CH), 4.65-4.50 (m, 2 H, CH_2), 4.20 (br s, 1 H, OH), 3.80-3 65 (m, 2 H, CH_2), 3.40 (s, 3 H, OCH_3), 1 45 (d, J = 6 Hz, 3 H, CH_3) - Anal calcd for $C_9H_{13}ClN_2O_3$ (**12a** + **12b**): C, 46 45, H, 5.59; N, 12 04 Found C, 46 8; H, 5.3, N, 11 7 - Analysis of the NMR spectrum indicated a ratio of **12a** : **12b** = 3 : 2

3-Chloro-5-(hydroxy)(phenyl)methyl-6-(2-methoxyethoxy)pyridazine (**13a**)
3-Chloro-4-(hydroxy)(phenyl)methyl-6-(2-methoxyethoxy)pyridazine (**13b**)
Table 2, Entry 4

General procedure with **4** (158 mg; 0 84 mmol), 1.6 M *n*-BuLi in hexane (1 15 ml; 1 84 mmol), TMP (0.31 ml, 1 84 mmol). The eluent was a 3 . 7 mixture of ethyl acetate and dichloromethane A mixture of **13a** and **13b** was obtained as a pale yellow solid (200 mg, 80%). - **13a**. ^{1}H NMR (60 MHz, $CDCl_3$) δ 7 55 (s, 1 H, H-4), 7 25 (s, 5 H, Ph), 5.85 (br s, 1 H, CH), 4.7-4.3 (m, 2 H, CH_2), 4 05 (br s, 1 H, OH), 3.9-3 5 (m, 2 H, CH_2), 3.3 (s, 3 H, OCH_3) - **13b** ^{1}H NMR (60 MHz, $CDCl_3$) δ 7 4 (s, 1 H, H-5), 7 25 (s, 5 H, Ph), 5.85 (br s, 1 H, CH), 4 7-4 3 (m, 2 H, CH_2), 4.05 (br s, 1 H, OH), 3.9-3 5 (m, 2 H, CH_2), 3 4 (s, 3 H, OCH_3). - Anal calcd for $C_{14}H_{15}ClN_2O_3$ (**13a** + **13b**)· C, 57 05, H, 5.09; N, 9 51. Found· C, 57.1, H, 5 2, N, 9.4 - Analysis of the NMR spectrum indicated a ratio of **13a** : **13b** = 3 · 2

3-(2-Methoxyethoxy)-4-(1-hydroxyethyl)pyridazine (**14a**)
Table 2, Entry 7

General procedure with **5** (195 mg, 1 27 mmol), 1 6 M *n*-BuLi in hexane (1 74 ml, 2 78 mmol), TMP (0.47 ml; 2 8 mmol) The eluent was a 3 7 mixture of ethyl acetate and dichloromethane Compound **14a** was obtained as a pale yellow solid (30 mg; 12%), mp 55°C (Tottoli). - ^{1}H NMR (60 MHz, $CDCl_3$) δ 8.8 (d, J_{5-6} = 5 Hz, 1 H, H-6), 7.55 (d, J_{5-6} = 5 Hz, 1 H, H-5), 5 1 (q, J = 6 Hz, 1 H, CH), 4 85-4 6 (m, 2 H, CH_2), 4 2-3 7 (m, 3 H, OH, CH_2), 3 45 (s, 3 H, OCH_3), 1 5 (d, J = 6 Hz, 3 H, CH_3) - Anal calcd for $C_9H_{14}N_2O_3$ C, 54.74; H, 7.07, N, 14 14. Found. C, 54.4, H, 6.7, N, 13 8

3-(2-Methoxyethoxy)-4-(hydroxy)(phenyl)methylpyridazine (**15a**)
Table 2, Entry 9

General procedure with **5** (214 mg, 1 39 mmol), 2 5 M *n*-Buli in hexane (2.20 ml; 5.50 mmol), TMP (0 91 ml, 5 40 mmol). The eluent was first pure dichloromethane, then a 1 . 1 mixture of dichloromethane and ethyl acetate, and finally pure ethyl acetate Compound **15a** was obtained as a brown solid (93 mg, 26%), mp 64°C - ^{1}H NMR (60 MHz, $CDCl_3$) δ 8 75 (d, J_{5-6} = 5 Hz, 1 H, H-6), 7 5 (d, J_{5-6} = 5 Hz, 1 H, H-5), 7 35 (br s, 5 H, Ph), 5.95 (s, 1 H, CH), 4 75-4.5 (m, 2 H, CH_2), 4 1 (br s, 1 H, OH), 3 9-3.55 (m, 2 H, CH_2), 3 35 (s, 3 H, OCH_3) - Anal calcd for $C_{14}H_{16}N_2O_3$ C, 64 61, H, 6 15, N, 10 77 Found C, 64 6; H, 5 8; N, 11 1

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