On the Metalation of 4-Substituted Pyridazines

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A series of new pyridazines bearing *ortho*-directing groups at C-4 (protected/activated amino or carboxylic acid functionalities) was prepared and their metalation with lithium 2,2,6,6-tetramethylpiperidide was studied. Reactions of the *ortho*-lithiated species thus obtained with aldehydes as electrophiles opens an access to 4,5-disubstituted pyridazines **3**, **4**, **14**, and **15**.

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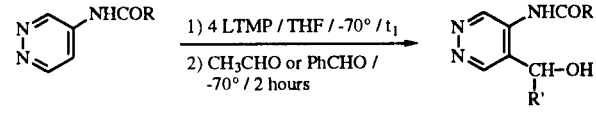
The continuing interest in the chemical and biological properties of pyridazine derivatives [1,2] has recently resulted in several studies concerning the introduction of carbon substituents into the 1,2-diazine system *via* the directed-lithiation route [3-5]. Whereas the successful use of metalation reactions of 3-substituted and 3,6-disubstituted pyridazines has been demonstrated, there have been no investigations of this reaction type with 4-substituted pyridazines so far. In the latter case, hydrogen abstraction, in principle, could be expected to occur at position 3, at position 5, or even at both positions. Here we wish to report on the utilization of pyridazines bearing *ortho*-directing groups at C-4 (NHCO-*t*-Bu, NHCOO-*t*-Bu, $CONHCH_2Ph$, CONH-*t*-Bu, dimethyloxazolinyl) as substrates for lithiation reactions, aiming at the investigation of the regiochemistry as well as of the synthetic usefulness of this approach for the preparation of *vic*-disubstituted pyridazines.

For the preparation of the pivalamide **1** and the carbamate **2**, 4-aminopyridazine [6,7] served as the starting material. This amino compound is conveniently accessible in one step from pyridazine (*via* a modified Chichibabin reaction), as described by Hara and van der Plas [7]. Compounds **1** and **2** can be obtained in high yields (83% and 99%, respectively), using pivaloyl chloride/triethylamine or BOC-anhydride as acylating agents. For the synthesis of the metalation educts **7**, **10**, and **13**, we started from 4-pyridazinecarboxylic acid [8] and the appropriate primary amine, using 1,1'-carbonyldiimidazole (CDI) as the coupling reagent. Applying this method, the yield of the previously described *N*-benzylcarboxamide **10** [9] could be significantly improved (71%) and, moreover, the sterically hindered *N*-*tert*-butylcarboxamide **13** now becomes accessible. Acid-catalyzed dehydration of an intermediate *N*-(2-hydroxy-1,1-dimethylethyl)-4-pyridazinecarboxamide afforded the oxazoline derivative **7** in 61% overall yield.

Metalation experiments with *N*-(4-pyridazinyl)-pivalamide (**1**) and *tert*-butyl *N*-(4-pyridazinyl)carbamate (**2**) were carried out at -70°, using a fourfold excess of lithium 2,2,6,6-tetramethylpiperidide (LTMP). In our previous investigations (metalation of 3-substituted pyridazines) [5], these conditions had been found to give the best results. The metalated species were treated with acetaldehyde or benzaldehyde as electrophile, the findings are given in Scheme I and Table I. Metalation of the carbamate **2**, followed by reaction with acetaldehyde or benzaldehyde, respectively, turned out to give only modest

Scheme I



1 R = *t*-Bu
2 R = O-*t*-Bu

3 R = *t*-Bu R' = CH_3
4 R = *t*-Bu R' = Ph
5 R = O-*t*-Bu R' = CH_3
6 R = O-*t*-Bu R' = Ph

Table I

Entry	Educt	t_1 [a]	Electrophile	Product	% yield	% recovery of starting material
1	**1**	2 h	CH_3CHO	**3**	43	11
2	**1**	2 h	PhCHO	**4**	63	–
3	**2**	3 h	CH_3CHO	**5**	20	13
4	**2**	3 h	PhCHO	**6**	23	8
5	**2**	2 h	PhCHO	**6**	25	5

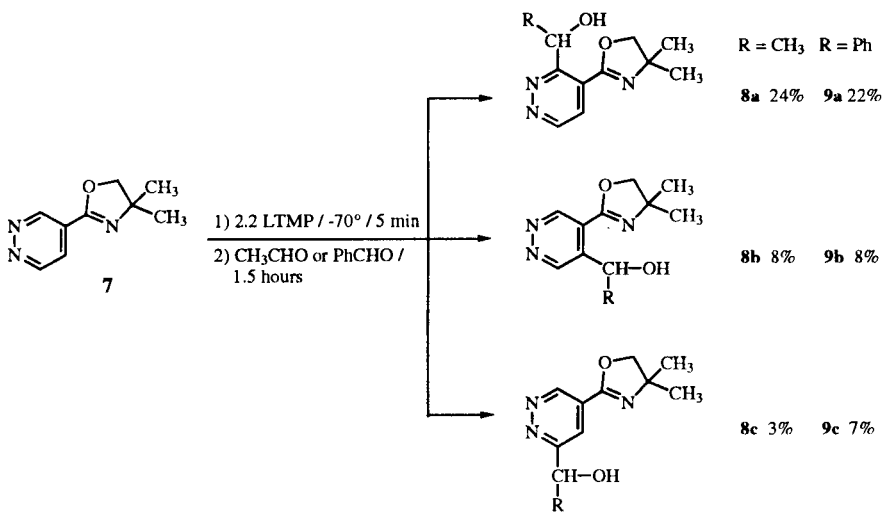
[a] Metalation time.

yields of *vic*-disubstituted pyridazines **5** and **6**. In contrast, the analogous carbinols **3** and **4** could be obtained in reasonable yields when the pivalamide **1** was employed as the educt for the metalation process. The position of the newly introduced substituent in compounds **3-6** at C-5 clearly follows from the ^{1}H nmr spectra. Interestingly, no regioisomeric products could be detected in the reaction mixtures, which indicates a high regioselectivity of the metalation process with the protected/activated 4-aminopyridazines **1** and **2**.

obtained upon quenching with acetaldehyde or benzaldehyde, respectively.

Surprisingly, with *N*-benzyl-4-pyridazinecarboxamide (**10**), the main product obtained upon lithiation and subsequent reaction with benzaldehyde turned out to be the *meta*-disubstituted pyridazine derivative **12a** which was obtained in 44% yield after column chromatography. As the sole *ortho*-disubstituted product, compound **12b** was isolated (see Scheme III). Employment of acetaldehyde as the electrophile resulted in a 1:1 mixture of the analogous

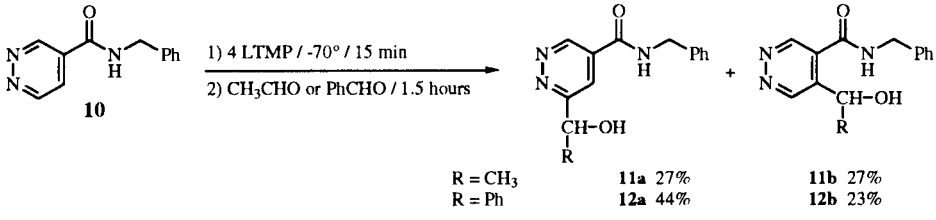
Scheme II



The results obtained on employment of a dimethyloxazolinyl moiety attached to C-4 of the 1,2-diazine system (compound **7**) as the directing group are summarized in Scheme II. In this case, the metalation time has to be kept as short as five minutes, since a significant decrease in the yields was observed on prolonged action of LTMP.

alcohols **11a** and **11b**. Similar to the findings with the oxazoline **7**, a metalation time of 2 hours leads to the formation of substantial amounts of polymeric material, whereas a combined yield of 54% for **11a,b** or 67% for **12a,b** can be achieved by choosing a lithiation time of only 15 minutes.

Scheme III

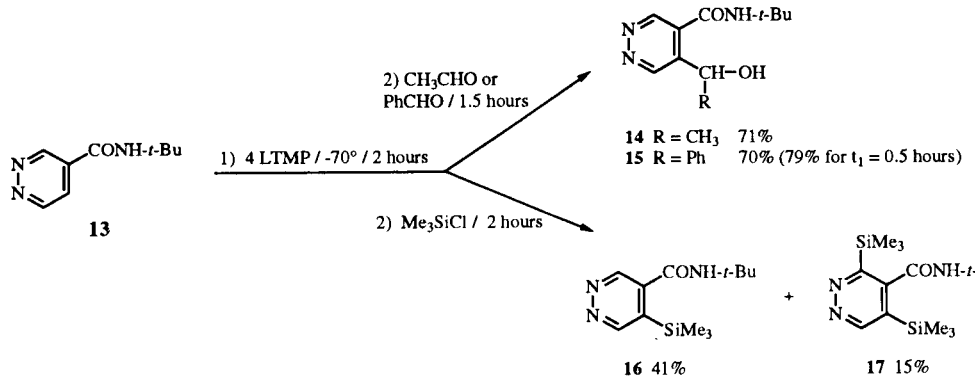


It should be emphasized that with the oxazoline **7**, the main products are the 3,4-disubstituted pyridazines **8a** and **9a**, whereas metalation at C-5 affording compounds **8b** and **9b** takes place only to a minor degree. Interestingly, in this case even small amounts of 4,6-disubstituted reaction products **8c** and **9c** were formed as indicated by the ^{1}H nmr spectra of the mixtures

Whereas, from a preparative point of view, the employment of an oxazolinyl moiety or a *N*-benzylcarboxamido function as *ortho*-directing groups in the 4-pyridazinyl series is of only low interest, utilization of the *N*-*tert*-butylcarboxamido group turned out to be a powerful instrument for the regioselective introduction of a carbon functional group into position 5 of the diazine system. This is demon-

strated by the preparation of the carbinols **14** and **15** from *N-tert*-butyl-4-pyridazinecarboxamide (**13**) in >70% yield, with no detectable amount of regioisomeric reaction products formed. In the case of compound **15**, it was found that a reduction of the metalation time from 2 hours to 30 minutes raises the yield from 70% to 79%.

Scheme IV



Interestingly, treatment of lithiated **13** with trimethylsilyl chloride as electrophile afforded 15% of a 3,4,5-trisubstituted pyridazine derivative (compound **17**) along with the expected monosilylated compound **16** as the main product (41%) (Scheme IV). The formation of **17** may be interpreted in terms of remetalation of compound **16** (or, less probably, of its 3-isomer) by an excess of LTMP, followed by another reaction with trimethylsilyl chloride which had remained unaffected by the metalating agent.

In summary, employment of a pivaloylamino group permits the regioselective introduction of a carbon substituent into position 5 of a 4-aminopyridazine system *via* the directed-lithiation route. For the introduction of such a functionality into C-5 of a 4-pyridazinecarboxylic acid, the utilization of an *N-tert*-butylcarboxamide function as *ortho*-directing group represents the method of choice. The unexpected regioselectivities encountered with the oxazoline **7** and the benzylamide **10** are currently under study in our laboratory.

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage microscope or on a Kofler block apparatus and are uncorrected. Infrared spectra were taken on a Jasco IRA-1 and on a Beckman 4250 spectrometer (potassium bromide pellets). The ^{1}H nmr spectra were recorded on a Bruker AC 80 (80 MHz), on a Jeol JNM-PMX 60 SI (60 MHz), or on a Bruker AC 200 (200 MHz) spectrometer in deuteriochloroform with tetramethylsilane 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; tetrahydrofuran was dried with a benzophenone-sodium mixture and distilled just before use.

N-(4-Pyridazinyl)pivalamide (**1**).

To an ice-cooled suspension of 1.07 g (11.3 mmoles) of 4-aminopyridazine [6,7] in 100 ml of dry dichloromethane were added 2.02 g (20 mmoles) of triethylamine, followed by 1.80 g (15 mmoles) of pivaloyl chloride, and the mixture was stirred for 10 minutes at 0° and for 1 hour at room temperature. The mixture was washed with saturated aqueous sodium hydrogencarbonate and with water, then it was dried and evaporated. Recrystallization from toluene gave 1.68 g (83%) of colorless crystals, mp 166°; ^{1}H nmr (80 MHz, deuteriochloroform): δ 9.24 (d, J = 2.6 Hz, H-3, 1 H), 8.99 (d, J = 6.0 Hz, H-6, 1 H), 8.74 (br s, NH, 1 H), 8.18 (dd, J_{3-5} = 2.6 Hz, J_{5-6} = 6.0 Hz, H-5, 1 H), 1.34 (s, CH_3, 9 H); ir: 2960, 1690, 1560, 1500, 1340, 1305, 1260, 1140 cm^{-1}.

Anal. Calcd. for $C_9H_{13}N_3O$: C, 60.31; H, 7.31; N, 23.44. Found: C, 60.17; H, 7.29; N, 23.34.

tert-Butyl *N*-(4-Pyridazinyl)carbamate (**2**).

To a suspension of 0.55 g (5.79 mmoles) of 4-aminopyridazine [6,7] in 50 ml of dry tetrahydrofuran were added 1.50 g (6.88 mmoles) of di-*tert*-butyl pyrocarbonate (BOC-anhydride), and the mixture was stirred for 1.5 hours at room temperature. The solvent was removed under reduced pressure and the residue was taken up in 70 ml of chloroform/2-propanol (9:1). The solution was washed with water, then it was dried and evaporated. Recrystallization from ethyl acetate/light petroleum afforded 1.12 g (99%) of a colorless powder, mp >172° dec; ^{1}H nmr (80 MHz, deuteriochloroform): δ 9.25 (d, J = 2.6 Hz, H-3, 1 H), 8.96 (d, J = 6.0 Hz, H-6, 1 H), 8.56 (br s, NH, 1 H), 7.93 (dd, J_{3-5} = 2.6 Hz, J_{5-6} = 6.0 Hz, H-5, 1 H), 1.54 (s, CH_3, 9 H); ir: 2960, 2750, 1710, 1610, 1565, 1530, 1360, 1320, 1240, 1150, 980, 830, 760 cm^{-1}.

Anal. Calcd. for $C_9H_{13}N_3O_2$: C, 55.37; H, 6.71; N, 21.52. Found: C, 55.65; H, 6.73; N, 21.30.

4-(4,4-Dimethyl-2-oxazolinyl)pyridazine (**7**).

To a suspension of 1.20 g (9.68 mmoles) of 4-pyridazinecarboxylic acid [8] in 70 ml of dry dichloromethane were added 2.07 g (12.78 mmoles) of 1,1'-carbonyldiimidazole and the mix-

ture was stirred at room temperature for 3 hours. After addition of 1.71 g (19.21 mmoles) of 2-amino-2-methylpropan-1-ol, stirring was continued for 1 hour. The solvent was removed under reduced pressure and the residue was purified by column chromatography (eluting with ethyl acetate/methanol, 8:2). The product obtained on evaporation of the eluate was taken up in 100 ml of toluene. Then 1.00 g (5.26 mmoles) of 4-toluenesulfonic acid monohydrate were added and the mixture was refluxed for 30 hours, using a Soxhlet apparatus which was charged with molecular sieve (4 Å). The solution was filtered and evaporated. Recrystallization from light petroleum yielded 1.05 g (61%) of pale yellow crystals, mp 82-83°; ^{1}H nmr (80 MHz, deuteriochloroform): δ 9.64 (dd, J_{3-5} = 2.1 Hz, J_{3-6} = 1.1 Hz, H-3, 1 H), 9.31 (dd, J_{3-6} = 1.1 Hz, J_{5-6} = 6.4 Hz, H-6, 1 H), 7.89 (dd, J_{3-5} = 2.1 Hz, J_{5-6} = 6.4 Hz, H-5, 1 H), 4.18 (s, CH_2, 2 H), 1.40 (s, CH_3, 6 H); ir: 2980, 1650, 1585, 1370, 1310, 1080, 970 cm^{-1}.

Anal. Calcd. for $C_9H_{11}N_3O$: C, 61.00; H, 6.26; N, 23.71. Found: C, 61.19; H, 6.22; N, 23.60.

N-Benzyl-4-pyridazinecarboxamide (**10**) [9].

To a suspension of 1.00 g (8.06 mmoles) of 4-pyridazinecarboxylic acid [8] in 60 ml of dry dichloromethane were added 1.70 g (10.46 mmoles) of 1,1'-carbonyldiimidazole and the mixture was stirred at room temperature for 3 hours. After addition of 1.30 g (12.15 mmoles) of benzylamine, stirring was continued for 1 hour. The solvent was removed under reduced pressure and the residue was purified by column chromatography (eluting with ethyl acetate/methanol, 19:1). Recrystallization from ethyl acetate/light petroleum gave 1.22 g (71%, lit [9] 52%) of colorless crystals, mp 82-84° (lit [9] 81°); ^{1}H nmr (80 MHz, deuteriochloroform): δ 9.45 (dd, J_{3-5} = 2.3 Hz, J_{3-6} = 1.1 Hz, H-3, 1 H), 9.17 (dd, J_{3-6} = 1.1 Hz, J_{5-6} = 6.4 Hz, H-6, 1H), 7.85 (dd, J_{3-5} = 2.3 Hz, J_{5-6} = 6.4 Hz, H-5, 1 H), 7.75 (br, NH, 1 H), 7.30 (s, C_6H_5, 5 H), 4.63 (d, J = 5.6 Hz, CH_2, 2 H); ir: 3360, 3020, 2930, 1650, 1580, 1500, 1290, 1260, 940, 740, 690 cm^{-1}.

N-tert-Butyl-4-pyridazinecarboxamide (**13**).

To a suspension of 1.00 g (8.06 mmoles) of 4-pyridazinecarboxylic acid [8] in 60 ml of dry dichloromethane were added 1.90 g (11.73 mmoles) of 1,1'-carbonyldiimidazole and the mixture was stirred at room temperature for 3 hours. After addition of 1.70 g (23.30 mmoles) of freshly distilled *tert*-butylamine, stirring was continued for 12 hours. The solvent was removed under reduced pressure and the residue was purified by column chromatography (eluting with ethyl acetate/methanol, 19:1). Recrystallization from light petroleum gave 0.55 g (38%) of pale yellow crystals, mp 153-154°; ^{1}H nmr (80 MHz, deuteriochloroform): δ 9.44 (d, unresolved, H-3, 1 H), 9.22 (d, J_{5-6} = 5.2 Hz, H-6, 1 H), 7.80 (dd, J_{3-5} = 2.3 Hz, J_{5-6} = 5.2 Hz, H-5, 1 H), 6.97 (br s, NH, 1 H), 1.48 (s, CH_3, 9 H); ir: 3240, 3040, 2940, 1650, 1520, 1430, 1310, 1205, 960, 860, 750 cm^{-1}.

Anal. Calcd. for $C_9H_{13}N_3O$: C, 60.31; H, 7.31; N, 23.44. Found: C, 60.56; H, 7.27; N, 23.53.

General Procedure for Metalation.

A solution of *n*-butyllithium in hexane (nx mmoles) was added at -30° to stirred anhydrous tetrahydrofuran (25 ml) under argon. Then 2,2,6,6-tetramethylpiperidine (nx mmoles) was added, the mixture was allowed to warm to 0° (15 minutes) and was kept at 0° for 30 minutes. The solution was then cooled to -70°. The pyridazine to metalate (x mmoles) was dissolved in dry tetrahydrofuran (85 ml) under argon and the solution was slowly added (5 minutes) to the metalation mixture. The metalation reaction was performed during t_1 at -70°, then the electrophile (nx mmoles, except for acetaldehyde which was used in excess) was added slowly (5 minutes). This reaction was performed during t_2 at -70°. The solution was then slowly hydrolyzed at -70° with a mixture of 2 *M* aqueous hydrochloric acid (2 ml), ethanol (4 ml), and tetrahydrofuran (4 ml) and warmed to 0°. A saturated solution of sodium hydrogencarbonate was added until neutralization 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 (unless otherwise stated).

N-[5-(1-Hydroxyethyl)-4-pyridazinyl]pivalamide (**3**).

Compound **1** was allowed to follow the general procedure (107 mg, 0.60 mmole), 1.6 *M n*-butyllithium in hexane (1.5 ml, 2.40 mmoles), 2,2,6,6-tetramethylpiperidine (0.41 ml, 2.43 mmoles), t_1 = 2 hours, acetaldehyde (1 ml, 17.9 mmoles), t_2 = 2 hours. Purification of the crude product by column chromatography on basic alumina (eluting with ethyl acetate/ethanol, 19:1) afforded compound **3** as a colorless solid, 58 mg (43%), mp 181°; ^{1}H nmr (60 MHz, deuteriochloroform): δ 10.35 (s, NH, 1 H), 10.10 (s, H-3, 1 H), 8.55 (s, H-6, 1 H), 6.75 (br s, OH, 1 H), 5.10 (q, J = 7 Hz, CH, 1 H), 1.55 (d, J = 7 Hz, CH_3, 3 H), 1.30 (s, *t*-Bu, 9 H). An amount of 15 mg (11 %) of starting material **1** was recovered.

Anal. Calcd. for $C_{11}H_{17}N_3O_2$: C, 59.17; H, 7.67; N, 18.82. Found: C, 59.4; H, 7.6; N, 18.6.

N-[5-(Hydroxy)(phenyl)methyl-4-pyridazinyl]pivalamide (**4**).

Compound **1** was allowed to follow the general procedure (120 mg, 0.67 mmole), 2.5 *M n*-butyllithium in hexane (1.07 ml, 2.68 mmoles), 2,2,6,6-tetramethylpiperidine (0.45 ml, 2.67 mmoles), t_1 = 2 hours, benzaldehyde (0.27 ml, 2.66 mmoles), t_2 = 2 hours. The eluent was first dichloromethane and then ethyl acetate. Compound **4** was obtained as a colorless solid, 120 mg (63%), mp 168°; ^{1}H nmr (60 MHz, deuteriochloroform): δ 10.15 (s, H-3, 1 H), 10.00 (br s, NH, 1 H), 8.60 (s, H-6, 1 H), 7.85 (br s, OH, 1 H), 7.25 (s, C_6H_5, 5 H), 6.00 (s, CH, 1 H), 1.20 (s, *t*-Bu, 9 H).

Anal. Calcd. for $C_{16}H_{19}N_3O_2$: C, 67.35; H, 6.71; N, 14.73. Found: C, 67.7; H, 6.5; N, 14.5.

tert-Butyl *N*-[5-(1-Hydroxyethyl)-4-pyridazinyl]carbamate (**5**).

Compound **2** was treated by the general procedure (122 mg, 0.62 mmole), 2.5 *M n*-butyllithium in hexane (1.0 ml, 2.50 mmoles), 2,2,6,6-tetramethylpiperidine (0.43 ml, 2.55 mmoles), t_1 = 3 hours, acetaldehyde (1 ml, 17.9 mmoles), t_2 = 2 hours. The eluent was ethyl acetate. Compound **5** was obtained as a colorless solid, 30 mg (20%), mp 142°; ^{1}H nmr (60 MHz, deuteriochloroform): δ 9.90 (s, H-3, 1 H), 9.00 (br s, NH, 1 H), 8.50 (s, H-6, 1 H), 6.60 (br s, OH, 1 H), 5.00 (q, J = 7 Hz, CH, 1 H), 1.55 (s + d, J = 7 Hz, *t*-Bu + CH_3, 12 H). An amount of 20 mg (13%) of starting material **2** was recovered.

Anal. Calcd. for $C_{11}H_{17}N_3O_3$: C, 55.22; H, 7.16; N, 17.56. Found: C, 55.3; H, 7.2; N, 17.3.

tert-Butyl *N*-[5-(Hydroxy)(phenyl)methyl-4-pyridazinyl]-carbamate (**6**).

Compound **2** was allowed to react following the general procedure (107 mg, 0.55 mmole), 2.5 *M n*-butyllithium in hexane (0.88 ml, 2.20 mmoles), 2,2,6,6-tetramethylpiperidine (0.37 ml, 2.19 mmoles), t_1 = 2 hours, benzaldehyde (0.22 ml, 2.19 mmoles), t_2 = 2 hours. The eluent was a 4:1 mixture of ethyl acetate and hexane. Compound **6** was obtained as a colorless solid, 42 mg (25%), mp 138°; ^{1}H nmr (60 MHz, deuteriochloroform): δ 9.85 (s, H-3, 1 H), 8.90 (br s, NH, 1 H), 8.35 (s, H-6, 1 H), 7.25 (s, C_6H_5, 5 H), 5.90 (m, CH + OH, 2 H), 1.50 (s, *t*-Bu, 9 H). An amount of 8 mg (5%) of starting material **2** was recovered.

Anal. Calcd. for $C_{16}H_{19}N_3O_3$: C, 63.77; H, 6.36; N, 13.94. Found: C, 63.8; H, 6.5; N, 13.8.

4-(4,4-Dimethyl-2-oxazolinyl)-3-(1-hydroxyethyl)pyridazine (**8a**). 4-(4,4-Dimethyl-2-oxazolinyl)-5-(1-hydroxyethyl)-pyridazine (**8b**). 4-(4,4-Dimethyl-2-oxazolinyl)-6-(1-hydroxyethyl)pyridazine (**8c**).

The three compounds above were obtained by allowing **7** to react following the general procedure (169 mg, 0.95 mmole), 1.6 *M n*-butyllithium in hexane (1.3 ml, 2.08 mmoles), 2,2,6,6-tetramethylpiperidine (0.35 ml, 2.07 mmoles), t_1 = 5 minutes, acetaldehyde (1 ml, 17.9 mmoles), t_2 = 1.5 hours. The eluent was a 49:1 mixture of ethyl acetate and methanol. A mixture of **8a**, **8b**, and **8c** was obtained as an orange oil, 74 mg (35%) of **8a** + **8b** + **8c**; ^{1}H nmr (200 MHz, deuteriochloroform): δ 9.47 (d, J_{3-5} = 2 Hz, H-3 (**8c**), 1 H), 9.43 (s, H-3 (**8b**), 1 H), 9.31 (s, H-6 (**8b**), 1 H), 9.22 (d, J_{5-6} = 5.2 Hz, H-6 (**8a**), 1 H), 8.03 (d, J_{3-5} = 2 Hz, H-5 (**8c**), 1 H), 7.84 (d, J_{5-6} = 5.2 Hz, H-5 (**8a**), 1 H), 6.38 (br s, OH (**8a** + **8b** + **8c**), 3 H), 5.47 (q, J = 6.6 Hz, CH (**8a**), 1 H), 5.19-5.12 (m, J = 6.6 Hz, CH (**8b** and **8c**), 2 H), 4.19 (s, CH_2 (**8b**), 2 H), 4.15 (s, CH_2 (**8a**), 2 H), 4.14 (s, CH_2 (**8c**), 2 H), 1.66 (d, J = 6.6 Hz, CH_3 (**8a**), 3 H), 1.58 (d, J = 6.6 Hz, CH_3 (**8b** + **8c**), 6 H), 1.40 (s, oxazolinyl CH_3 (**8a** + **8b** + **8c**), 18 H). Analysis of the ^{1}H nmr spectrum indicated a ratio of **8a**:**8b**:**8c** = 8:2.5:1.

Anal. Calcd. for $C_{11}H_{15}N_3O_2$ (**8a** + **8b** + **8c**): C, 59.71; H, 6.83; N, 18.99. Found: C, 59.6; H, 7.0; N, 18.9.

4-(4,4-Dimethyl-2-oxazolinyl)-3-[(hydroxy)(phenyl)methyl]-pyridazine (**9a**). 4-(4,4-Dimethyl-2-oxazolinyl)-5-[(hydroxy)-(phenyl)methyl]pyridazine (**9b**). 4-(4,4-Dimethyl-2-oxazolinyl)-6-[(hydroxy)(phenyl)methyl]pyridazine (**9c**).

The reaction of **7** under the conditions of the general procedure were (163 mg, 0.92 mmole), 1.6 *M n*-butyllithium in hexane (1.3 ml, 2.08 mmoles), 2,2,6,6-tetramethylpiperidine (0.35 ml, 2.07 mmoles), t_1 = 5 minutes, benzaldehyde (0.23 ml, 2.3 mmoles), t_2 = 1.5 hours. The eluent was ethyl acetate. A mixture of **9a**, **9b** and **9c** was obtained as an orange oil, 97 mg (37%) of **9a** + **9b** + **9c**: ^{1}H nmr (200 MHz, deuteriochloroform): δ 9.49 (d, J_{3-5} = 2 Hz, H-3 (**9c**), 1 H), 9.48 (s, H-3 (**9b**), 1 H), 9.30 (d, J_{5-6} = 5.2 Hz, H-6 (**9a**), 1 H), 9.08 (s, H-6 (**9b**), 1 H), 7.94 (d, J_{3-5} = 2 Hz, H-5 (**9c**), 1 H), 7.85 (d, J_{5-6} = 5.2 Hz, H-5 (**9a**), 1 H), 7.30-7.20, (m, C_6H_5 (**9a** + **9b** + **9c**),15 H), 6.57 (s, CH (**9a**), 1 H), 6.12 (s, CH (**9c**), 1 H), 6.07 (s, CH (**9b**), 1 H), 4.21-3.77 (m, CH_2 + OH (**9a** + **9b** + **9c**), 9 H), 1.42-1.15 (m, CH_3 (**9a** + **9b** + **9c**), 18 H). Analysis of the ^{1}H nmr spectrum indicated a ratio of **9a**:**9b**:**9c** = 3:1:1.

Anal. Calcd. for $C_{16}H_{17}N_3O_2$ (**9a** + **9b** + **9c**): C, 67.83; H, 6.05; N, 14.83. Found: C, 67.5; H, 5.9; N, 15.2.

N-Benzyl-6-(1-hydroxyethyl)-4-pyridazinecarboxamide (**11a**). *N*-Benzyl-5-(1-hydroxyethyl)-4-pyridazinecarboxamide (**11b**).

Compound **10** under the conditions of the general procedure provided **11a** and **11b** as follows: (147 mg, 0.69 mmole), 1.6 *M n*-butyllithium in hexane (1.7 ml, 2.72 mmoles), 2,2,6,6-tetramethylpiperidine (0.47 ml, 2.78 mmoles), t_1 = 15 minutes, acetaldehyde (1 ml, 17.9 mmoles), t_2 = 1.5 hours. The eluent was a 19:1 mixture of ethyl acetate and methanol. A mixture of **11a** and **11b** was obtained as an orange oil, 96 mg (54%) of **11a** + **11b**: ^{1}H nmr (200 MHz, deuteriochloroform): δ 9.16 (d, J_{3-5} = 2 Hz, H-3 (**11a**), 1 H), 9.01 (s, H-3 (**11b**), 1 H), 8.85 (s, H-6 (**11b**), 1 H), 8.67 (t, J = 5.7 Hz, NH (**11a** or **11b**), 1 H), 8.38 (t, J = 5.7 Hz, NH (**11a** or **11b**), 1 H), 8.00 (d, J_{3-5} = 2 Hz, H-5 (**11a**), 1 H), 7.28 (m, C_6H_5 (**11a** + **11b**), 10 H), 5.09-5.01 (m + br s, CH + OH (**11a** + **11b**), 4 H), 4.57 (d, J = 5.7 Hz, CH_2 (**11a** + **11b**), 4 H), 1.45 (d, J = 6.6 Hz, CH_3 (**11a** or **11b**), 3 H), 1.41 (d, J = 6.6 Hz, CH_3 (**11a** or **11b**), 3 H). Analysis of the ^{1}H nmr spectrum indicated a ratio of **11a**:**11b** = 1:1.

Anal. Calcd. for $C_{14}H_{15}N_3O_2$ (**11a** + **11b**): C, 65.36; H, 5.88; N, 16.33. Found: C, 65.6; H, 6.1; N, 15.9.

N-Benzyl-6-(hydroxy)(phenyl)methyl-4-pyridazinecarboxamide (**12a**). *N*-Benzyl-5-(hydroxy)(phenyl)methyl-4-pyridazinecarboxamide (**12b**).

Using the general procedure compound **10** provided **12a** + **12b** as follows: (148 mg, 0.69 mmole), 1.6 *M n*-butyllithium in hexane (1.75 ml, 2.80 mmoles), 2,2,6,6-tetramethylpiperidine (0.47 ml, 2.78 mmoles), t_1 = 15 minutes, benzaldehyde (0.30 ml, 2.95 mmoles), t_2 = 1.5 hours. The eluent was ethyl acetate. Compound **12a** was obtained as an orange oil, 97 mg (44%); ^{1}H nmr (200 MHz, deuteriochloroform): δ 9.13 (d, J_{3-5} = 1.8 Hz, H-3, 1 H), 8.30 (t, J = 5.6 Hz, NH, 1 H), 7.98 (d, J_{3-5} = 1.8 Hz, H-5, 1 H), 7.18 (m, C_6H_5, 10 H), 5.98 (s, CH, 1 H), 5.69 (br s, OH, 1 H), 4.44 (d, J = 5.6 Hz, CH_2, 2 H). Compound **12b** was obtained as an orange oil, 51 mg (23%); ^{1}H nmr (200 MHz, deuteriochloroform): δ 8.89 (s, H-3, 1 H), 8.80 (s, H-6, 1 H), 8.42 (t, J = 5.5 Hz, NH, 1 H), 7.27 (m, C_6H_5, 10 H), 6.08 (s, CH, 1 H), 5.72 (br s, OH, 1 H), 4.45 (d, J = 5.5 Hz, CH_2, 2 H).

Anal. Calcd. for $C_{19}H_{17}N_3O_2$ (**12a** + **12b**): C, 71.46; H, 5.37; N, 13.16. Found: C, 71.7; H, 5.6; N, 12.8.

N-tert-Butyl-5-(1-hydroxyethyl)-4-pyridazinecarboxamide (**14**).

Compound **13** was allowed to react under the conditions of the general procedure (156 mg, 0.87 mmole), 1.6 *M n*-butyllithium in hexane (2.20 ml, 3.52 mmoles), 2,2,6,6-tetramethylpiperidine (0.59 ml, 3.50 mmoles), t_1 = 2 hours, acetaldehyde (1 ml, 17.9 mmoles), t_2 = 1.5 hours. The eluent was ethyl acetate. Compound **14** was obtained as a brown oil, 138 mg (71%); ^{1}H nmr (200 MHz, deuteriochloroform): δ 9.00 (s, H-3, 1 H), 8.75 (s, H-6, 1 H), 7.95 (br s, NH, 1 H), 5.10 (q, J = 7.0 Hz, CH, 1 H), 4.95 (s, OH, 1 H), 1.45 (s, *t*-Bu, 9 H).

Anal. Calcd. for $C_{11}H_{17}N_3O_2$: C, 59.17; H, 7.67; N, 18.82. Found: C, 59.6; H, 7.6; N, 18.3.

N-tert-Butyl-5-(hydroxy)(phenyl)methyl-4-pyridazine-carboxamide (**15**).

Compound **13** was allowed to react under the conditions of the general procedure (162 mg, 0.90 mmole), 1.6 *M n*-butyllithium in hexane (2.25 ml, 3.60 mmoles), 2,2,6,6-tetramethylpiperidine (0.60 ml, 3.56 mmoles), t_1 = 2 hours, benzaldehyde (0.37 ml, 3.64 mmoles), t_2 = 30 minutes. The eluent was ethyl acetate. Compound **15** was obtained as a pale yellow solid, 203 mg (79%), mp 132°; ^{1}H nmr (200 MHz, deuteriochloroform): δ 9.00

(s, H-3, 1 H), 8.90 (s, H-6, 1 H), 7.87 (br s, NH, 1 H), 7.33 (s, C_6H_5, 5 H), 6.12 (m, CH + OH, 2 H), 1.34 (s, *t*-Bu, 9 H).

Anal. Calcd. for $C_{16}H_{19}N_3O_2$: C, 67.35; H, 6.71; N, 14.73. Found: C, 67.6; H, 6.9; N, 14.3.

N-tert-Butyl-5-trimethylsilyl-4-pyridazinecarboxamide (**16**). *N-tert*-Butyl-3,5-bis(trimethylsilyl)-4-pyridazinecarboxamide (**17**).

The above two compounds were obtained following the general procedure from **13** (153 mg, 0.85 mmole), 1.6 *M n*-butyllithium in hexane (2.14 ml, 3.42 mmoles), 2,2,6,6-tetramethylpiperidine (0.58 ml, 3.44 mmoles), t_1 = 2 hours, trimethylsilyl chloride (0.43 ml, 3.39 mmoles), t_2 = 2 hours. The eluent was a 3:7 mixture of ethyl acetate and dichloromethane. Compound **16** was obtained as a colorless solid, 87 mg (41%), mp 194°; ^{1}H nmr (200 MHz, deuteriochloroform): δ 9.14 (d, $J_{3\text{-}6}$ = 1.1 Hz, H-3, 1 H), 8.92 (d, $J_{3\text{-}6}$ = 1.1 Hz, H-6, 1 H), 6.75 (br s, NH, 1 H), 1.47 (s, *t*-Bu, 9 H), 0.37 (s, $SiMe_3$, 9 H).

Anal. Calcd. for $C_{12}H_{21}N_3OSi$: C, 57.33; H, 8.42; N, 16.71. Found: C, 57.4; H, 8.1; N, 16.5.

Compound **17** was obtained as a colorless solid, 42 mg (15%), mp 184°; ^{1}H nmr (60 MHz, deuteriochloroform): δ 9.05 (s, H-6, 1 H), 5.65 (br s, NH, 1 H), 1.50 (s, *t*-Bu, 9 H), 0.50 (s, $SiMe_3$, 9 H), 0.45 (s, $SiMe_3$, 9 H).

Anal. Calcd. for $C_{15}H_{29}N_3OSi_2$: C, 55.68; H, 9.03; N, 12.99. Found: C, 55.4; H, 9.5; N, 12.7.

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