Metalation of Diazines. VI. Metalation of Pivaloylaminopyrazine and *N*-*t*-Butylpyrazinamide. Unusual Regioselectivity in the Metalation Reaction

A. Turck, N. Plé, D. Trohay, B. Ndzi and G. Quéguiner*

Laboratoire de Chimie Organique Fine et Hétérocyclique,
URA 1429, INSA-IRCOF, BP 08,
76131 Mt St Aignan Cedex, France

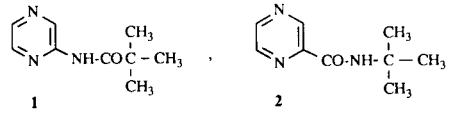
Received December 18, 1991

Metalation of pivalamidopyrazine and *N*-*t*-butylpyrazinamide were studied. For pivalamido pyrazine the yields were poor and some addition products were isolated. The metalation of *t*-butylpyrazinamide was successful and a curious regioselectivity was highlighted.

J. Heterocyclic Chem., **29**, 699 (1992).

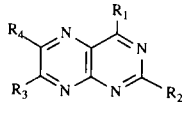
Introduction.

Until now only chloro and methoxy groups had been used to direct the metalation reaction in the pyrazine series [1-3]. So it is obvious that the extension of the scope of the reaction to other *ortho*-directing group could be interesting. The metalation of pivaloylamino pyrazine **1** and *N*-*t*-butylpyrazinamide **2** is described and an unusual regioselectivity in the metalation reaction is studied:



1 **2**

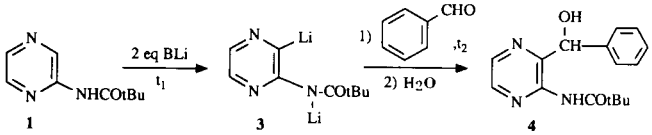
Metalation of compounds **1** and **2** could afford *ortho*-disubstituted derivatives of amino and carboxy pyrazines which could be effective intermediates in the synthesis of pteridines for example:



Metalation of Pivalamidopyrazine **1**.

As seen before, directed metalation of amino derivatives is an interesting goal. In the benzene series, Gschwend [4] has proposed the use of the pivaloylamino group to induce *ortho*-metalation and in the pyridine series it was successfully used by Güngör [5].

Metalation was tested first with various metalating agents and benzaldehyde as an electrophile. Conditions are summarized in Table I.



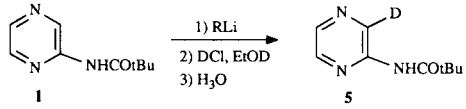
1 **3** **4**

Table I

Metalating agents	θ	t_1 [c] hours	Results
1 *n*-BuLi/TMEDA	-70	1	unisolated products (mainly nucleophilic addition)
2 mesityllithium	-70	1.5	90% of **1** recovered
3 mesityllithium	-25	0.5	70% of **1** recovered + **6** (<5%)
4 mesityllithium	0	0.5	50% of **1** recovered, 24% of **6**
5 *t*-Buli	-70	1.5	63% of **7**
6 LTMP	-70	1	100% of **1** recovered
7 LTMP	-25	1	80% of **1** recovered
8 LTMP	0	1	25% of **4**

[a] t_1: metalation time: t_2: reaction time (1.5 hour); equivalent amounts of metalating agent (2.2); LTMP: lithium 2,2,6,6-tetramethylpiperidide; TMEDA: tetramethylethylenediamine.

The last experiment provided the expected alcohol **4** with a 25% yield. As this yield was too low another set of experiments was performed (Table II). In order to quench the lithio derivative a solution of deuterium chloride in deuterioethanol was used.



1 **5**

2

Table II

Metalating agents	Equivalent amount	Solvent	θ	t_1 [c] hours	Results
LTMP [a]	3	THF	-70	2	**1** recovered
LTMP [a]	4	THF	0	1.5	25% of **5**
BuLi +TMP	2.1 0.05	THF	0	1	**1** recovered
BuLi +TMP	2.1 0.1	THF	20	2	10% of **5**
BuLi +TMP	2.1 0.1	Ether	0	2	**1** recovered

[a] TMP: 2,2,6,6-tetramethylpiperidine.

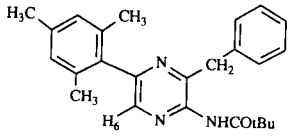
Even with a great excess of LTMP we could not improve the yield of metalation (25%). Experiments with a catalytic amount of TMP in the butyllithium solution (a method which gave good results in the pyridine series [6]) was also unsuccessful.

These poor results may depend on the low reactivity of **1** *versus* the metalating agent, the amino group deactivating the nucleus hydrogens. Furthermore the tendency of the pyrazine nucleus to undergo nucleophilic addition precludes the use of more powerful metalating agents like alkyllithium as this was observed in the first set of experiments (Table I).

Determination of the Structures of **6** and **7**.

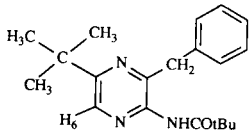
The ^1H nmr spectrum indicated in the molecule the presence of mesityl for **6** (or *t*-butyl for **7**), a benzyl group and a pyrazinic hydrogen are present in both compound **6** and **7**.

To determine the position of the benzyl groups on the pyrazine nucleus a high field nmr spectrum (400 MHz) was performed. In the literature [7], it was demonstrated that the coupling constants between a CH_2 group and an hydrogen of pyrazine were: 0.62 (*para*); 0.36 (*meta*); 0.70 (*ortho*). The value observed between H_6 and the methylenic protons for **6** was 0.60 Hz indicating a *para* coupling. In order to verify that it was the right coupling an irradiation of the methylene group was performed and the signal of the pyrazine hydrogen H_6 became, as predicted, a singlet in place of a triplet. The absence of the signal near 9.5 ppm proves that there was no hydrogen in *ortho* position of the pivalamido group. So the structure of **6** was:



6

A similar analysis led us to the following structure **7**:



7

Metalation of *N*-*t*-Butylpyrazinamide **2**.

Metalation was first performed with LTMP at 0° and the lithio derivative was quenched with a deuterium chloride, deuterioethanol mixture affording compound **8**. The equivalent amount of LTMP was determinant. The deuteration yield was 5% with 2,3 equivalents and 75% with 4 equivalents.

The same experiment performed at −70° afforded two isomers **8** and **9**. The yields of the two isomers were determined at different temperatures (Table III).

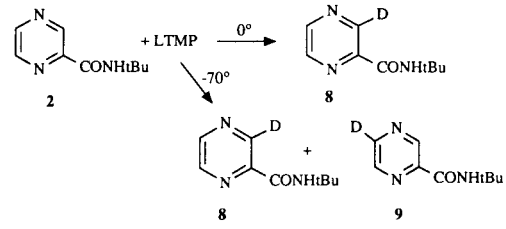


Table III

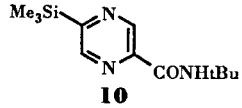
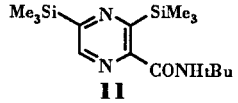
Temperature	-80°	-70°	-30°	0°
yields **8** *ortho*-isomer	25%	25%	70%	75%
yields **9** *para*-isomer	45%	40%	0%	0%

At low temperature the *para* isomer is the main product and above −30° the *ortho*-isomer is the sole product. To test the reversibility of the lithiation, the following experiment was performed: metalation at −70° (4 equivalents, 2 hours, THF) then the reaction mixture was warmed to 0° and kept 1 hour at this temperature: the *ortho* compound **8** is obtained with a 74% yield, quite close to the result of Table IV at 0° (75%).

These results prompt us to consider the *para*-derivative **9** as the kinetic product and the *ortho*-derivative **8** as the thermodynamic one.

If our hypothesis is valuable a reaction performed under the conditions of an "equilibrium shift" [8] with chlorotrimethylsilane as an electrophile must give the *para* derivative whatever be the temperature. The results are given in Table IV.

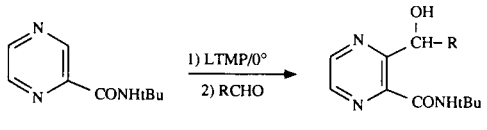
Table IV

	-70°	-30°	0°
 **10**	77%	31%	0%
 **11**	0%	41%	67%

No monosubstituted *ortho*-silylated product was observed even at low temperature so it may be supposed that the disilylated compound **11** resulted from the metalation of **10** in the reaction medium.

It must be noticed that, under kinetic conditions, the carboxamido *ortho*-directing group actually orientates the metalation in *para*-position with pyrazinamide what is, at least, an unusual result.

Acetaldehyde and benzaldehyde were reacted at 0° affording *ortho*-substituted alcohols **12** and **13**.



R = CH_3 **12** y = 45 %
R = Ph **13** y = 43 %

EXPERIMENTAL

All manipulations were carried out under argon. All reagents were freshly distilled. Tetrahydrofuran was dried with a benzophenone-sodium mixture and distilled just before use. The ir spectra were recorded on a Beckman 4250 spectrometer. All ir spectra were performed in potassium bromide. The nmr spectra were recorded on a Varian EM 360 L or Bruker 200 MHz spectrometer. All nmr spectra were carried out with deuteriochloroform solutions and δ are given in ppm. Microanalysis were performed with a Carlo Erba 1106 apparatus. Melting points were determined with a Kofler hot-stage microscope.

3-Phenylhydroxymethyl-2-pivaloylaminopyrazine **4**.

Reactions were performed in a 100 ml three-necked flask equipped with a magnetic stirring bar, a pentane thermometer, and two septa. A stream of argon was maintained for 30 minutes. A 50 ml syringe was used to introduce 40 ml of dry tetrahydrofuran or ether (water content <40 ppm) and the solution was cooled to $-30°$ and 2 ml (3.2 mmoles) of *n*-butyllithium 1.6 *M* in hexane and 0.50 ml (3.3 mmoles) of 2,2,6,6-tetramethylpiperidine were introduced. The mixture was allowed to warm to 0° and kept at this temperature for 30 minutes.

A solution of the amide **1** (0.25 g, 1.4 mmoles) in 2 ml of tetrahydrofuran was introduced from a syringe. After 1 hour reaction at 0°, the electrophile: benzaldehyde (0.45 ml, 4.42 mmoles) was added and the mixture kept 1.5 hours at 0°. The hydrolysis was performed with a mixture of 1 ml of water and 4 ml of ethanol. Tetrahydrofuran was evaporated and the aqueous phase was extracted three times with 25 ml of chloroform. The extract was dried over magnesium sulphate then evaporated, the brown oil was purified by chromatography on silica gel with a 1/1 mixture of dichloromethane and ethyl acetate. A tan solid (0.1 g, 25%) was obtained, mp 77°; ^{1}H nmr: δ 1.13 (s, 9H, *t*-Bu), 1.35 (m, 1H, OH), 5.97 (m, 1H, CH), 7.25 (m, 6H, H phenyl, NH), 8.75 (m, 2H, H pyrazine); ir: ν 3310, 1700, 1590, 1500, 1455, 1150 cm^{-1}.

Anal. Calcd. for $C_{16}H_{19}N_3O_2$ (M = 285.3): C, 67.35; N, 14.72; H, 6.70. Found: C, 67.1; N, 14.6; H, 7.0.

3-Deuterio-2-pivaloylaminopyrazine **5**.

In the same reaction vessel as above 40 ml of tetrahydrofuran was added. After cooling to $-30°$, 3.5 ml (5.6 mmoles) of a solution of butyllithium in hexane (1.6 *M*) and 1 ml (5.9 mmoles) of 2,2,6,6-tetramethylpiperidine were introduced from a syringe. This mixture was warmed to 0° and kept 0.5 hour at this temperature. Pivaloylaminopyrazine **1** (0.25 g, 1.4 mmoles) was added and the metalation was performed during 1.5 hours at 0°. Then a mixture of 0.5 ml of deuterium chloride and 0.5 ml of deuterated ethanol was added and the mixture was stirred 0.5 hour. Thereafter the solution was hydrolysed and treated as above, 0.21 g (87%) of product was recovered which was a mixture of unreacted pivaloylaminopyrazine **1** (75%) and deuterated product **5** (25%). The percentage was determined by analysis of the nmr spectrum in which H_3 (9.60 ppm) is very easy to identify.

3-Benzyl-5-mesityl-2-pivaloylaminopyrazine **6**.

A 40 ml solution of tetrahydrofuran was cooled to $-70°$; at this temperature 3.4 ml (5.8 mmoles) of *t*-butyllithium in pentane (1.7 *M*) and 0.45 ml (2.9 mmoles) of 2-bromomesitylene were added. A white precipitate of lithium bromide soon appeared and the solution was kept under stirring 1 hour at $-70°$. The mixture was warmed to 0° and the amide **1** (0.23 g, 1.3 mmoles) was added. After 0.5 hour of metalation at 0°, benzaldehyde (0.3 ml, 2.9 mmoles) was introduced and the mixture stirred 1.5 hours at 0°. Then hydrolysis was performed with a mixture of 1 ml of water and 4 ml of ethanol. Solvents were evaporated and the aqueous residue extracted three times with chloroform. The extracts were dried over magnesium sulphate, evaporated and the residue was purified by chromatography on silica gel with dichloromethane as eluent; 0.121 g (24%) of **6** was recovered as a colorless oil; ^{1}H nmr: δ 1.05 (s, 9H, *t*-Bu), 1.97 (s, 6H, $2CH_3$ mesityl), 2.33 (s, 3H, CH_3 mesityl), 4.27 (s, 2H, CH_2), 7.00 (s, 2H, H mesityl), 7.40 (s, 6H, H phenyl + NH), 8.22 (s, 1H, H pyrazine); ir: ν 3420, 2960, 1700, 1500, 1440, 1370, 1135 cm^{-1}.

Anal. Calcd. for $C_{25}H_{29}N_3O$ (M = 387.5): C, 77.49; N, 10.84; H, 7.54. Found: C, 77.6; N, 10.7; H, 7.5.

3-Benzyl-5-*t*-butyl-2-pivaloylaminopyrazine **7**.

t-Butyllithium (2.5 ml, 4.3 mmoles) was introduced in 40 ml of tetrahydrofuran at $-70°$. A solution of pivaloylaminopyrazine (0.35 g, 12.95 mmoles) in 2 ml of tetrahydrofuran was added at $-70°$ and stirring was continued for 1.5 hours. Benzaldehyde (2.5 ml, 5 mmoles) was then added and reacted 1.5 hours at this temperature. Hydrolysis was performed with a mixture of 1 ml of hydrogen chloride, 4 ml ethanol and 5 ml tetrahydrofuran at $-70°$. After warming to 10° the solution was neutralized with sodium hydrogenocarbonate. Solvents were evaporated and the aqueous phase extracted three times with 25 ml of chloroform. After drying over magnesium sulphate, evaporation and silica gel chromatography with a 1/1 mixture of dichloromethane and ethyl acetate, 0.4 g (63%) of a pale orange solid **7** was obtained, mp 110°; ^{1}H nmr: δ 1.38 (s, 18H, 2 *t*-Bu), 4.12 (s, 2H, CH_2), 7.27 (s, 5H, H phenyl), 7.80 (m, 1H, NH), 8.12 (s, 1H, H pyrazine); ir: ν 3300, 2960, 1660, 1500, 1480 cm^{-1}.

Anal. Calcd. for $C_{20}H_{27}N_3O$ (M = 325.43): C, 73.82; N, 12.91; H, 8.25. Found: C, 73.8; N, 12.9; H, 8.3.

3-Deuterio-2-*N*-*t*-butylpyrazinamide **8**.

Same procedure as for **5**. A white solid was obtained (0.19 g, 76%). Analysis of the nmr spectrum of this solid showed that it was constituted of 75% of **8** and 25% of reacted product **2**; ^{1}H nmr: δ 1.55 (s, 9H, *t*-Bu), 7.80 (m, 1H, NH), 8.50 (d, 1H, H_6), 8.75 (d, 1H, H_5), $J_{5\text{-}6}$ = 2.5 Hz.

5-Trimethylsilyl-2-*N*-*t*-butylpyrazinamide **10**.

The metalating agent was prepared as for **4** and the solution was cooled to $-70°$. Then a mixture of **2** (0.25 g, 1.4 mmoles), trimethylchlorosilane (0.7 ml, 5.6 mmoles) and tetrahydrofuran (3 ml) was introduced slowly in the flask. After 2 hours at $-70°$ hydrolysis was done at this temperature with a mixture of 1 ml of hydrogen chloride, 2 ml of tetrahydrofuran and 2 ml of ethanol. After warming to 10° neutralization was effected with a saturated solution of sodium hydrogenocarbonate. Solvents were evaporatated and the aqueous solution extracted three times with di-

chloromethane. After drying and evaporation the product was purified by chromatography on silica gel with mixture of 70% hexane and 30% ethyl acetate as the eluent. It was then sublimated (90° 1 mm Hg) and **10** was obtained as a white solid (0.27 g, 77%), mp 93°; ^{1}H nmr: δ 0.3 (s, 9H, $SiMe_3$), 1.3 (s, 9H, *t*-Bu), 7.75 (m, 1H, NH), 8.55 (d, 1H, H_6), 9.48 (d, 1H, H_3), J_{3-6} = 1.6 Hz; ir: ν 3380, 1675, 1525 cm^{-1}.

Anal. Calcd. for $C_{12}H_{21}N_3OSi$ (M = 251.3): C, 57.33; N, 16.71; H, 8.42. Found: C, 57.3; N, 16.4; H, 8.7.

3,5-Bis-trimethylsilyl-2-*N*-*t*-butylpyrazinamide **11**.

Same procedure as for **10** except the reaction temperature was 0° and the eluent was a 9/1 mixture of hexane and ethyl acetate. Compound **11** was obtained as a yellow liquid (0.3 g, 67%); ^{1}H nmr: δ 0.35 (s,, 9H, $SiMe_3$), 0.40 (s, 9H, $SiMe_3$), 1.45 (s, 9H, *t*-Bu), 7.80 (m, 1H, NH), 8.50 (s, 1H, H_6); ir: ν 3380, 2960, 1685, 1515, 1365 cm^{-1}.

Anal. Calcd. for $C_{15}H_{29}N_3OSi_2$ (M = 323.4): C, 55.66; N, 12.99; H, 8.97. Found: C, 56.0; N, 12.7; H, 8.8.

2-*N*-*t*-Butylpyrazinamide)-1-ethanol **12**.

Same procedure as for **4**; the electrophile was acetaldehyde (2 ml, 35 mmoles). After usual workup and a chromatography on silica gel with a 4/1 mixture of dichloromethane and ethyl acetate as eluent, a pale yellow solid was obtained, **12** (0.14 g, 45%), mp 70°; ^{1}H nmr: δ 1.5 (s, 9H, *t*-Bu), 5.47 (m, 2H, CH-OH), 8.02 (m, 1H, NH), 8.47 (d, 1H, H_6), 8.68 (d, 1H, H_5), J_{5-6} = 2.5 Hz; ir: ν 3440, 3330, 2980, 1650, 1530, 1450, 1360 cm^{-1}.

Anal. Calcd. for $C_{11}H_{17}N_3O_2$ (M = 223.2): C, 59.14; N, 18.82; H, 7.62. Found: C, 58.6; N, 18.6; H, 7.6.

3-Phenylhydroxymethyl-2-*N*-*t*-butylpyrazinamide **13**.

Same procedure as for **4**; after the usual workup the product was purified by chromatography on silica gel with a 8/1 mixture of dichloromethane and ethyl acetate. A yellow solid **13** was obtained, (0.17 g, 43%), mp 67°; ^{1}H nmr: δ 1.3 (s, 9H, *t*-Bu), 6.35 (dd, 2H, CHOH), 7.2 (m, 5H, phenyl), 7.6 (m, 1H, NH), 8.3 (d, 1H, H_6), 8.55 (d, 1H, H_5); ir: ν 3320, 2970, 1650, 1570, 1550, 1450, 1050 cm^{-1}.

Anal. Calcd. for $C_{16}H_{19}N_3O_2$ (M = 285.2): C, 67.32; N, 14.73; H, 6.66. Found: C, 67.2; N, 14.4; H, 6.8.

REFERENCES AND NOTES

[1] A. Turck, L. Mojovic and G. Guéguiner, *Synthesis*, 881 (1988).

[2] A. Turck, D. Trohay, L. Mojovic, N. Plé and G. Quéguiner, *J. Organometal. Chem.*, **412**, 301 (1991).

[3] R. J. Mattson and C. P. Sloan, *J. Org. Chem.*, **55**, 3410 (1990).

[4] W. Furher and H. W. Gschwend, *J. Org. Chem.*, **44**, 1133 (1979).

[5] T. Güngor, F. Marsais and G. Quéguiner, *J. Organometal. Chem.*, **215**, 139 (1981).

[6] F. Trécourt, M. Mallet, F. Marsais and G. Quéguiner, *J. Org. Chem.*, **53**, 1367 (1988).

[7] A. F. Bramwell G. Riezebos, R. D. Wells, *Tetrahedron Letters*, 2489 (1971).

[8] Equilibrium shift: simultaneous introduction of the electrophile and the compound to metalate in a solution of the metalating agent.