Pergamon

Tetrahedron 55 (1999) 5389–5404

TETRAHEDRON

Functionalization by Metalation of the Benzene Moiety of Benzodiazines. Determination of structures by Long-Range ^{1}H -^{15}N Correlation at Natural Abundance. Diazines XXV.

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Received 28 October 1998; accepted 3 March 1999

Abstract

The first lithiation of the benzene moiety of various quinazolinones, quinoxalines, and phthalazines has been performed. The effects of kind and positions of various directing groups towards the regioselectivity of the metalation have been studied. Unambiguous structure determinations of quinoxaline derivatives have been carried out by applying NMR GHMBC ^{1}H-^{15}N sequence.

Keywords : metalation / benzodiazines / NMR

INTRODUCTION

The benzodiazine skeletons are commonly found in compounds exhibiting a wide range of biological activities. Among them, the molecules based on quinazoline[1-6] or 4(3*H*)-quinazolinone [7-9] ring systems received much attention because of their interesting medicinal and agricultural properties. Construction of benzodiazines involves cyclization of appropriately substituted benzenes whose synthesis is not always easy. This is the reason why functionalization *via* metalation of the benzene moiety could provide a consistent strategy for the synthesis of new benzodiazines.

In previous papers, we have mentioned the lithiation of the benzene moiety of cinnolines [10] and studied in detail the functionalization by metalation of the benzene ring system of various quinazolines.[11] In these two cases, it was highlighted an exceptional and unexpected reactivity towards metalation at the C_8 position, *peri* to the ring nitrogen atom. Moreover, the presence of a substituent inducing *ortho*-directed metalation on the benzene moiety such as a chlorine atom or a methoxy group favored the lithiation reaction.

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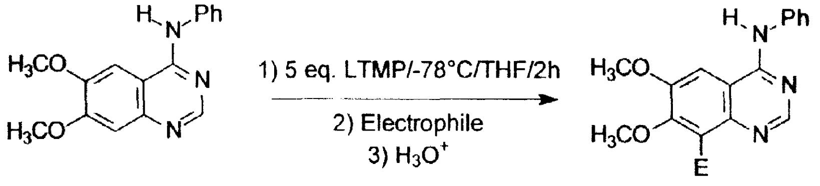
PII: S0040-4020(99)00202-1

We report here the functionalization *via* the metalation reaction of 4-anilino-6,7-dimethoxyquinazoline which exhibits a highly selective inhibition of the tyrosine kinase activity.[1,12] Then, we have extended our study to the first metalation of the benzene moiety of quinazolinones and quinoxalines which all present a *peri* ring nitrogen atom. In order to determine whether the presence of a *peri* ring nitrogen atom was absolutely necessary to achieve lithiation of the benzene moiety, metalation of phthalazines was also tested.

RESULTS

Among various quinazolines and related compounds which have recently been prepared and evaluated for their ability to inhibit the tyrosine kinase activity,[1,12] 4-anilino-6,7-dimethoxyquinazoline **1** was one of the most effective compounds. As we have already described the metalation of various substituted quinazolines at the C_8 position,[11] we have decided to use this methodology in order to synthesize new 8-substituted derivatives.

Lithium 2,2,6,6-tetramethylpiperidide (LTMP) in excess (5 equivalents) was chosen as the metalating agent. As a matter of fact, one equivalent of LTMP was added to trap the labile proton of the amino group, and then four additional equivalents of LTMP were necessary to achieve lithiation of the benzene moiety.[11] So treatment of **1** with LTMP at -78°C for 2 hours followed by reaction with two different aldehydes as the electrophile afforded 8-substituted quinazolines **2** and **3** in very good yields (Scheme 1).



1

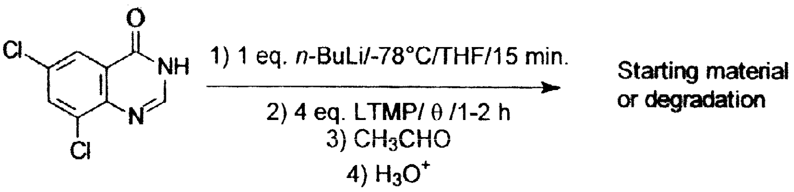
2 E = $CH_3CH(OH)$ 91%
3 E = PhCH(OH) 85%

Scheme 1

Many 4(3*H*)-quinazolinone derivatives are well-known as biologically active compounds as Prazosin[9] or Methaqualone.[13] The easy lithiation of the benzene cycle of 4-alkoxy- or 4-aminoquinazolines[11] prompted us to attempt metalation of various 4(3*H*)-quinazolinones.

Recently, some papers reported the *ortho*-directing effect of the amide function, thus allowing the regioselective lithiation of the pyridine ring of 2(1*H*)-quinolinone.[14,15] Lithiation of 3-acylamino-4(3*H*)-quinazolinones as well as 2-alkyl-3-amino-4(3*H*)-quinazolinones[16] has been reported. In these cases, metalation occurred at the C_2 position, if free, or on the α carbon of the 2-alkyl group. To our knowledge, no lithiation of the benzene moiety in these series has been described.

To determine the relative influence on lithiation of the ring nitrogen atom and the *ortho*-directing groups of the benzene moiety, 6,8-dichloro-, 7-chloro- and 6,7-dimethoxy-4(3*H*)-quinazolinones **4**, **5** and **6** have been tested (Schemes 2 and 3).

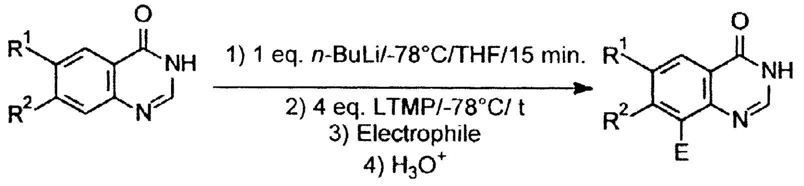


4

Scheme 2

Various attempts to metalate 6,8-dichloro-4(3*H*)-quinazolinone **4** have been performed. In the first step, the labile proton of the lactam function was trapped by action of one equivalent of *n*-BuLi at -78°C for 15 minutes, as mentioned by Smith *et al.*[16] Then 4 equivalents of LTMP were added with various reaction times (1 to 2 hours) and temperatures (-78°C to 0°C), before reaction with acetaldehyde as the electrophile. At low temperature (-78°C), starting material was recovered. When the temperature was increased to 0°C, only degradation compounds were observed.

Lithiation of 7-chloro-4(3*H*)-quinazolinone **5** or 6,7-dimethoxy-4(3*H*)-quinazolinone **6** was performed with one equivalent of *n*-BuLi at -78°C, followed by reaction of LTMP in excess (4 equivalents) for 1 h at -78°C. The C_8 lithiated species were quenched by acetaldehyde or benzaldehyde as the electrophile to give the secondary alcohols **7-8** (from substrate **5**) and **9-10** (from substrate **6**) beside small amounts of starting material (Scheme 3).



5 $R^1 = H, R^2 = Cl$

6 $R^1 = R^2 = OCH_3$

			t
7	E = $CH_3CH(OH)$	73%	1 h
8	E = PhCH(OH)	95%	"
9	E = $CH_3CH(OH)$	50%	2 h
10	E = PhCH(OH)	50%	"

Scheme 3

Compounds **5** and **6**, where the C_8 position *peri* to $N_{(1)}$-ring nitrogen was free, could be lithiated. Their reactivity was close to the one previously observed with the related 4-methoxyquinazolines,[11] which underwent lithiation at the C_8 position and led to 8-substituted quinazolines with slightly better yields.

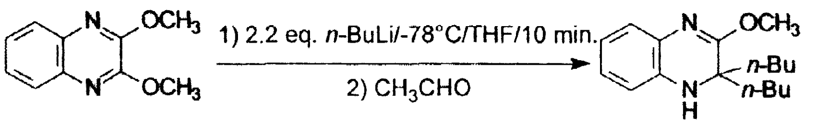
For compound **4**, no reaction occurred and degradation compounds or starting material were recovered. It must be reminded that the related 6,8-dichloro-4-methoxyquinazoline [11] had been functionalized *via* the metalation reaction between the two chlorine atoms at the C_7 position. These results indicated that the pyrimidinone ring made the benzene moiety of the quinazolinone quite less reactive towards lithiation than the related 4-methoxyquinazoline.

Regarding overall results obtained with quinazolines and 4(3*H*)-quinazolinones, it could appear that the presence of a ring nitrogen atom was essential to perform a *peri* lithiation.

To check such a hypothesis, we have tested the lithiation of the benzene ring of quinoxaline derivatives, which have two ring nitrogen atoms at the *peri* positions.

First experiments were performed with 2,3-dimethoxyquinoxaline **11** which possesses two free *peri* positions but no *ortho*-directing group on the benzene moiety.

When **11** was treated with 4 equivalents of LTMP at -78°C and reacted with acetaldehyde or trimethylsilyl chloride as the electrophile, only starting material was recovered. When the temperature was increased to 0°C, degradation products were observed beside starting material. When *n*-BuLi (2.2 equivalents) was used at -78°C, an addition compound **12** was obtained in good yield (88%) (Scheme 4).

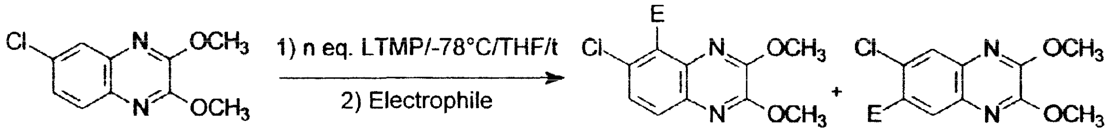


11 **12** **88%**

Scheme 4

Analysis of ^1H and ^{13}C NMR spectra points out that compound **12** results from nucleophilic addition of two molecules of *n*-BuLi on the pyrazine moiety. Moreover, NMR spectra indicate that the butyl groups are equivalent and could be on the same carbon, thus allowing us to conclude that compound **12** has the above-mentioned structure.

Adding an *ortho*-directing group on the benzene moiety could improve reactivity towards lithiation. That is the reason why 6-chloro-2,3-dimethoxyquinoxaline **13**, which presents two free *peri* positions and a chlorine atom at C_6 on the benzene ring system, has been chosen. To avoid addition reactions with the metalating agent, lithiation was performed with LTMP. Treatment of **13** with LTMP at –78°C for a reaction time t, followed by reaction with various electrophiles afforded 5-substituted quinaxolines **14a-16a** as major products, beside low amounts of 7-substituted quinoxaline **14b** and starting material (Scheme 5, Table 1).



13 **14a-16a** **14b**

Scheme 5

n eq.	Reaction time (h)	Electrophile	Starting material	Product	(yield %)
2.2	0.5	CH_3CHO	46%	**14a** (47%)	**14b** (7%)
4.0	0.5	CH_3CHO	6%	**14a** (81%)	**14b** (13%)
4.0	1	PhCHO	-	**15a** (85%)	-
4.0	1	CH_3I	39%	**16a** (51%)[a]	-

a) recovering of a mixture of starting material **13**/**16a**/**16c** (39% /51%/10%) where **16 c** is 6-chloro-7-ethyl-2,3-dimethoxy-quinoxaline

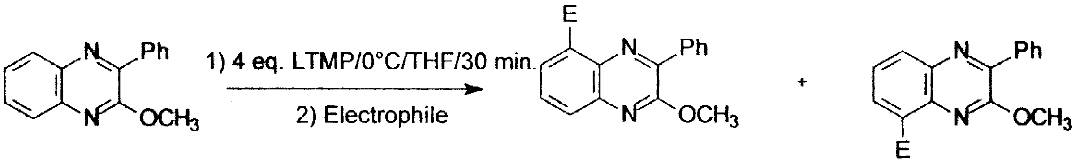
Table 1

The results given in Table 1 revealed that a large excess of LTMP was necessary to improve the yields. Lithiation occurred preferably at the C_5 position, *peri* to a ring nitrogen atom and *ortho* to the chlorine atom. With acetaldehyde as the electrophile, small amounts of C_7 isomer **14b** are observed. In the case of methyl iodide, the kinetic acidity of the methylene group inserted at the C_8 position was undoubtedly sufficient for further lithiation and alkylation by giving the ethyl compound **16c**.

The higher regioselectivity at C_5 was due to the additive effects of the *ortho*-directing chlorine atom and that of the *peri* ring nitrogen atom.

It should be interesting to observe if the substitution of a methoxy group by a phenyl group on the diazine moiety could also allow lithiation of the unsubstituted benzene moiety. It could be assumed that a phenyl group could improve the stability of the intermediate lithio derivative. So metalation of 2-methoxy-3-phenylquinoxaline **17** has been achieved with LTMP as the metalating agent.

In this case, the two *peri* positions C_5 and C_8 could undergo lithiation (Scheme 6).



17 **18a-20a** **18b-19b**

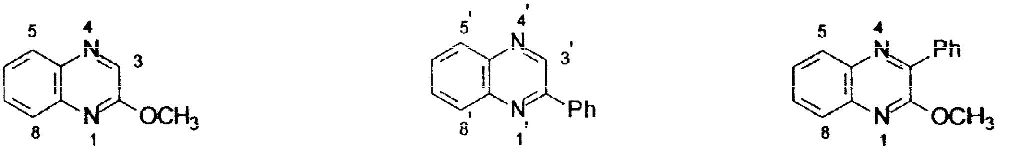
$E = CH_3CH(OH)^a$	**18a**	42%	**18b**	8%
$E = PhCH(OH)^a$	**19a**	44%	**19b**	19%
$E = Si(CH_3)_3^{a,b,c}$	**20a**	65%	-	

a) recovering of starting material
b) obtained with the 'in situ trapping technique'
c) recovering of 5,8-di(trimethylsilyl)-2-methoxy-3-phenylquinoxaline **20c** (10%)

Scheme 6

A first attempt with 2.2 equivalents of LTMP at –78°C for 30 minutes afforded only starting material. The most efficient metalation conditions have been established with 4 equivalents of base and 30 minutes of reaction time at 0°C. Under these experimental conditions, a mixture of 5- and 8-substituted quinoxalines (**18-20**) was obtained beside starting material.

Structure elucidation of compounds **18-20** has been carried out by applying gradient-enhanced HMBC sequence optimized for observation of long-range ^1H – ^{15}N heteronuclear couplings at natural abundance. First of all, the unequivocal ^{15}N assignments of **17** must have been performed. Such unambiguous assignments of ^{15}N chemical shifts were based on ^2J (^1H-^{15}N) interactions in proton-coupled nitrogen spectra of 2-methoxyquinoxaline **21** and 2-phenylquinoxaline **22**.



21 22 **17**

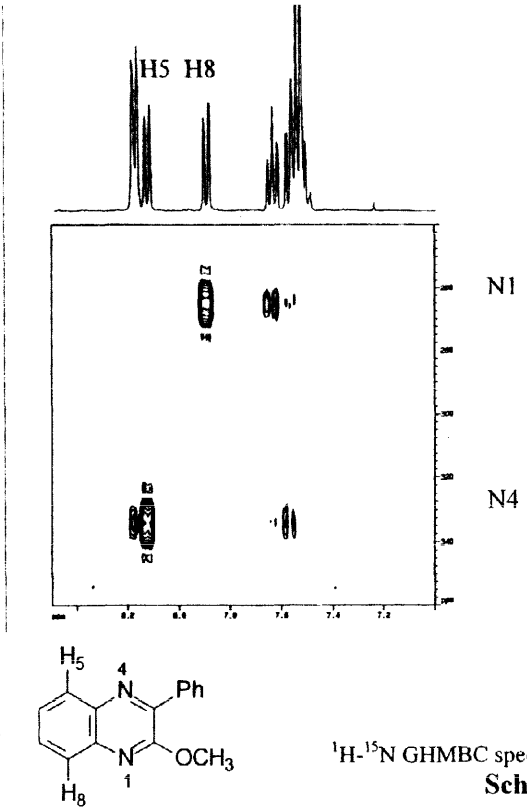
Scheme 7

The values of $^2J(^1H\text{-}^{15}N)$ previously established for some azines were given in a range from 9.8 to 14.4 Hz.[17]

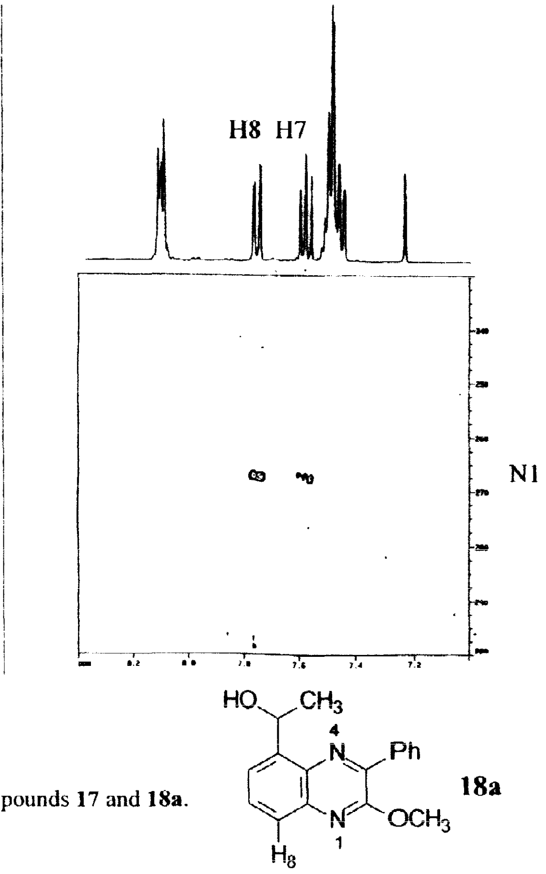
The ^{15}N NMR spectrum of **21** presented two signals : a singlet at 262 ppm assigned to N_1 and a doublet at 339 ppm (J = 10.5 Hz) for N_4.

The spectrum of **22** showed a singlet at 319 ppm for $N_{1'}$ and a doublet at 332 ppm (J = 10.5 Hz) for $N_{4'}$. It can be noted that a replacement of an hydrogen by a methoxy group at the α position causes a high shielding increase, whereas the shielding effect of the phenyl group is moderate.The ^{15}N NMR spectrum of **17** showed two singlets which could be allocated at 265 ppm for N_1 and 334 ppm for N_4.

To allow an unambiguous structure elucidation for compounds **18–20**, it was necessary to determine the chemical shifts of hydrogens H_5 and H_8. The ^1H NMR spectrum of **17** showed two doublets of doublet at 8.13 ppm and 7.89 ppm (J = 8.2 Hz and J = 1.2 Hz) which could be assigned equally to H_5 and H_8. Moreover these *peri* hydrogens were coupled with N_1 or N_4 by a long-range ^3J ($^1H\text{-}^{15}N$) coupling constant. Such $^1H\text{-}^{15}N$ long-range coupling has been observed and determined for about 3–3.5 Hz during elucidation of alkaloid structures such as Ajmaline and Cryptolepine containing indole[18,19] or indoloquinoline[20,21] skeletons. The respective chemical shifts of H_5 and H_8 have been clearly allocated by applying gradient-enhanced long-range $^1H\text{-}^{15}N$ (GHMBC) heteronuclear shift correlation. The HMBC–base pulse sequence described by G.E. Martin with a long-range delay optimized for 3 Hz[21] has been used. Correlations were observed from N_1 resonance at 265 ppm to H_8 at 7.89 ppm and N_4 resonance at 334 ppm to H_5 at 8.13 ppm. Weaker correlations were also noticed between N_1 and H_7 (at 7.64 ppm) and between N_4 and H_6 (at 7.54 ppm) and the H_α of the phenyl group (Scheme 8).



17



18a

$^1H\text{-}^{15}N$ GHMBC spectra of compounds **17** and **18a**.
Scheme 8

This preliminary and unambiguous assignment allowed us to determine the structure of compounds **18-20**. The signal at 7.80 ppm for **18a** and **19a** and at 7.85 ppm for **20a** gave a correlation with N_1 resonance at 268-266 ppm, whereas for compounds **18b** and **19b** the doublet of doublet at 8.02 ppm had a high correlation with N_4 resonance at 336 ppm. These results enabled us to conclude that metalation occurred at the C_5 position for compounds **18-20(a)** and at the C_8 position for compounds **18b** and **19b**. With trimethylsilyl chloride as the electrophile, a 5,8-di(trimethylsilyl) compound **20c** was obtained in 10 % yield. In this case, H_6 and H_7 appeared as an AB spectrum. The doublet at 7.76 ppm gave a weak correlation with N_1 at 268 ppm and could be allocated to H_7.

So, for the first time in the quinoxaline series, acquisition of ^1H-^{15}N GHMBC spectra provides an efficient method to elucidate the structures of quinoxalines, for which the symmetrical position of the two ring nitrogens N_1 and N_4 makes difficult the differentiation of the *peri* hydrogens H_5 and H_8 as well as for the carbons C_9 and C_{10}. Such a method could be extended to the allocation of 2,3-disubstituted pyrazine structures.

If the deprotonation of compound **17** was thermodynamically controlled, the relative amounts of the two isomers substituted at C_5 or C_8 could be explained by the heats of formation of the lithiated species and could be examined in a simple approach to account for the regioselectivity. The heats of formation of lithiated intermediates could be calculated by semi-empirical methods.

Semi-empirical Li/PM3 method which appears to be one of the most efficient methods for calculations of systems containing lithium[22] has been used. The Li/PM3 results are usually in satisfactory agreement with the energetic ordering and structural data obtained from *ab initio* calculations.[23,24] The analysis of heats of formation of lithio derivatives indicates that the C_5 lithiated compound is more stable than the one metalated at C_8 and is in accordance with the experimental results (Scheme 9).

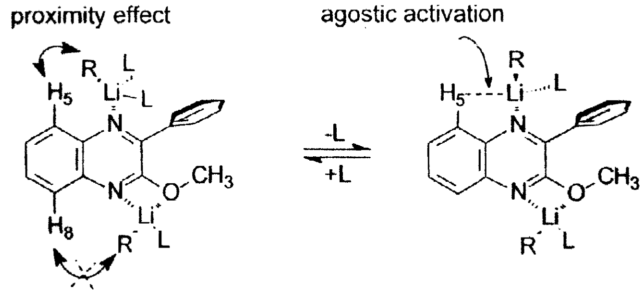
ΔHf = + 68.6 kcal/mol ΔHf = + 71.3 kcal/mol

Heats of formation by Li/PM3

Scheme 9

A steric hindrance factor could also be taken into account. As previously mentioned,[11] a complexation of the metalating agent between the oxygen of the methoxy group and the N_1 ring nitrogen could occur. In this case, the geometry of the mixed aggregate is blocked in a conformation preventing the deprotonation of the C_8 position. However, chelation of the lithiated base with the N_4 ring nitrogen favors the deprotonation of the C_5 position by agostic activation or complex-induced proximity effects[25-30] (Scheme 10).

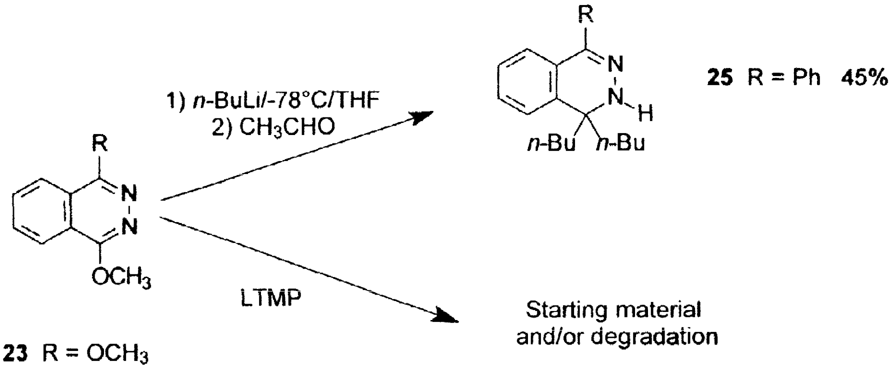
Scheme 10



R : LTMP
L : solvent

A last question could be asked : was it absolutely necessary to have a *peri* ring nitrogen atom to achieve the lithiation of the benzene moiety of benzodiazine ? Lithiation of phthalazine could provide the answer to such a question.

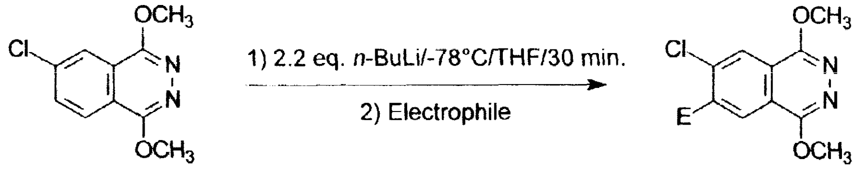
Attempts to metalate 1,4-dimethoxyphthalazine **23** were made with different alkyllithiums or LTMP as the metalating agent. Whatever the conditions, starting material was recovered beside degradation products. Experiments were performed with 1-methoxy-4-phenylphthalazine **24** with *n*-BuLi or LTMP as the metalating agent. With *n*-Buli at – 78°C, only addition product **25** was obtained, whereas with LTMP all attempts failed and degradation products were solely recovered beside starting material (Scheme 11).



Scheme 11

It could be assumed that presence of an *ortho*-directing group such as a chlorine atom on the benzene moiety could favor the lithiation. So, 6-chloro-1,4-dimethoxyphthalazine **26** was chosen for this study, and *n*-BuLi was tested as the metalating agent.

Treatment of compound **26** with 2.2 equivalents of *n*-BuLi at –78°C for 30 minutes, followed by reaction with various electrophiles allowed us to prepare 7-substituted phthalazines **27-30** in good yields (Scheme 12).



26

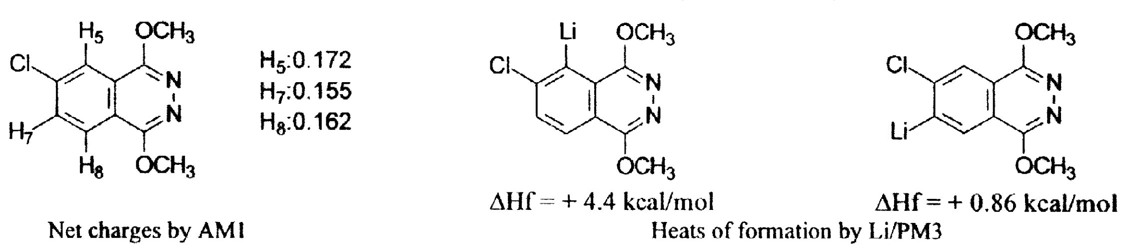
27 E = $CH_3CH(OH)$ 89%
28 E = PhCH(OH) 78%
29 E = CH_3 53%[a]
30 E = I 83%

(a) recovering of a mixture of 29/26 (proportions : 63/37; yield : 53%/47%)

Scheme 12

These results indicated that, if a ring nitrogen atom was not always essential to induce metalation on the benzene moiety, the deprotonation occurred only if an *ortho*-directing group, making the metalation easier, was placed on the benzene ring.

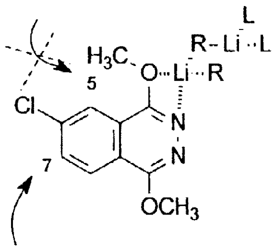
Regioselectivity of the lithiation could be discussed in terms of kinetic or thermodynamic control of the reaction using semi-empirical calculations. In the case of kinetic control, analysis of the net charges of H_5, H_7 and H_8 could be considered in first approximation, although such calculations do not take into account possible complexations and steric effects. The net charges determined by AM1 method are different, H_5 and H_8 being slightly more electropositive than H_7, thus indicating that a kinetic deprotonation could occur either at the C_5 or C_8 positions, which is in disagreement with the experimental results. If deprotonation is thermodynamically controlled, heats of formation determined by semi-empirical Li/PM3 method could be examined as a simple approach to account for the regioselectivity. Li/PM3 calculations of heats of formation of lithiated derivatives were carried out (Scheme 13).



Scheme 13

Preliminary considerations on the stability of the lithiated derivatives indicate that the C_7 lithiated intermediate is the more stable isomer, which is in agreement with the experimental results.

As for the quinoxaline derivative **17**, the steric hindrance hypothesis could also be considered. Complexation of the lithiated species with the oxygen of the methoxy group and the N_3 ring nitrogen induces a repulsion of the methyl group towards the C_5 *peri* position, thus avoiding the deprotonation of this position and favoring the one of the C_7 position (Scheme 14, R : alkyl, L : solvent).



Scheme 14

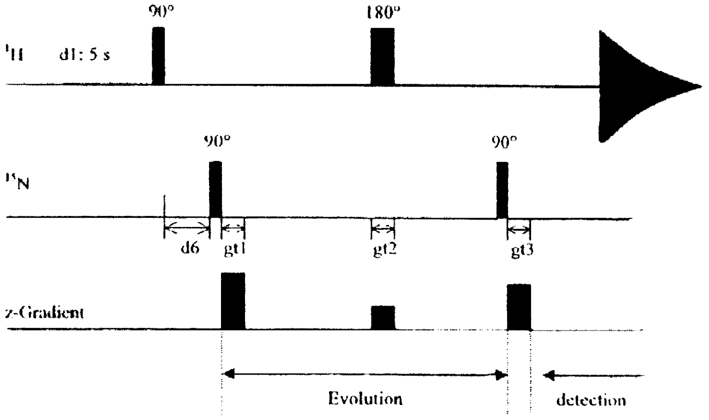
CONCLUSION

Direct lithiation of the benzene moiety of various benzodiazines has been studied and achieved. The presence of *ortho*-directing groups such as chlorine atom or methoxy group on the benzene cycle favored lithiation, which took usually place on the *peri* position to a ring nitrogen atom.

Lithiation of the benzene moiety of quinoxaline without *ortho*-directing group has been successfully performed when the diazine ring was substituted by a phenyl group. In this case, elucidation of structures has been established by long-range ^1H-^{15}N heteronuclear shift correlations at natural abundance using gradient-enhanced inverse detection. This efficient method, used for the first time in these series, allowed us to determine the structures of the functionalized quinoxalines and could be extended to the pyrazine series, which are often difficult to elucidate because of their symmetry. It was also highlighted that if a ring nitrogen was not always needed to achieve the lithiation of the benzene moiety, the presence of an *ortho*-directing group on the benzene ring system appeared to be absolutely necessary.

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage. The ^1H and ^{13}C NMR spectra were recorded in deuteriochloroform on a Bruker AC 200 instrument. The ^{15}N NMR spectra were recorded in deuteriochloroform on a Bruker ARX 400 instrument (internal reference : nitromethane). The one and two-dimensional NMR spectra were obtained at 298K with a probehead Broad-Band inverse 5 mm. The pulse sequence used is HMBC. The long-range ^1H-^{15}N delay (d6) was optimized as a function of $1/2J_{N\text{-}H}$ (^3J=3Hz, d6 :166.7 ms). Pulsed fields gradients, gt1-gt3, had uniform rise times and durations of 1 ms. The experiment was performed with a gradient ratio of 7 : 3 : 5.



Microanalyses were performed on a Carlo Erba CHNOS 1160 apparatus. The IR spectra were obtained as potassium bromide pellets with a Perkin Elmer FTIR 1650 spectrophotometer. Mass spectra were recorded at 70 eV (EI) on a JEOL JMS-AX 500 spectrometer.

THF 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 water). Metalations were performed under an argon atmosphere. Reagents were handled with syringes through septa. All reagents were of commercial quality and were purchased from Aldrich Chemical Co. or Acros.

The following benzodiazines were synthesized according to the literature: 6,7-dimethoxy-4-phenylaminoquinazoline **1** and 6,7-dimethoxy-4(3*H*)-quinazolinone **6** [1], 6,8-dichloro-4(3*H*)-quinazolinone **4**,[31] 7-chloro-4(3*H*)-quinazolinone **5**,[32] 2,3-dimethoxyquinoxaline **11**, [33] 6-chloro-2,3-dimethoxyquinoxaline **13**,[34] 2-chloro-3-phenylquinoxaline,[35] 2-methoxyquinoxaline **21**,[36], 2-phenylquinoxaline **22**,[37] 1,4-dimethoxyphthalazine **23**,[38] 4-phenyl-1(2*H*)-phthalazinone [39] and 6-chloro-1,4-dihydroxyphthalazine.[40]

Procedure A for direct lithiation by lithium 2,2,6,6-tetramethylpiperidide

A solution of *n*-butyllithium (1.6 M or 2.5 M in hexane) was added to cold (-50°C), stirred and anhydrous THF (15 mL) under an atmosphere of dry argon. Then 2,2,6,6-tetramethylpiperidine (TMPH) was added. The mixture was warmed to 0°C. After 20 minutes, the mixture temperature was then carried to the temperature θ_1 and the benzodiazine dissolved in 5 mL of THF added. After a time t_1 at θ_1, the electrophile was introduced and stirring was continued for a time t_2 at θ_2. Hydrolysis was then carried out at θ_2 using a solution of 35% aqueous hydrochloric acid, ethanol and THF (1/4/5) for θ_2 = -78°C. For a temperature of 0°C , the hydrolysis solution was a mixture of water (2 mL) and ethanol (8 mL). At room temperature, the mixture was made slightly basic with saturated sodium hydrogen carbonate solution. When the electrophile was iodine, the solution was decolorized with sodium thiosulphate and evaporated nearly to dryness. The residue was extracted with dichloromethane (3x15 mL), the combined organic extracts were then dried over magnesium sulphate and evaporated. The crude product was purified by column chromatography on silica gel followed by sublimation.

Procedure B for "in situ trapping" metalation

After preparation of the lithiated base (LTMP) similarly to procedure A, the mixture temperature was carried to θ. The benzodiazine dissolved in 5 mL of THF and trimethylsilyl chloride were simultaneously introduced and the mixture was stirred for a time t at θ. The following steps are similar to procedure A.

Procedure C for direct lithiation by alkyllithium

A solution of *n*-butyllithium (1.6 M in hexane) was added slowly to the benzodiazine dissolved in cold (-78°C), stirred and anhydrous THF (15 mL) under an atmosphere of dry argon. The mixture was allowed to stand at -78°C for t_1. The electrophile was introduced and stirring was continued for a time t_2 at -78°C. Hydrolysis and the following steps are similar to procedure A.

Typical procedure for formation of chlorophthalazine intermediates :

Dry phthalazinone (or 1,4-dihydroxyphthalazine) (1 g) and phosphorus pentachloride (1-2 eq.) in phosphorus oxychloride (50 mL) were refluxed until the hydroxy-compound dissolved (1-5 h). Boiling was continued for a further 10 h. The solvent was removed under reduced pressure, the residue dissolved in dichloromethane was poured on ice and treated with potassium carbonate. The solution was extracted with dichloromethane (3x15 mL), the combined organic extracts were dried over magnesium sulphate and evaporated under reduced pressure at 40°C. After flash column chromatography (silica, eluent : petroleum ether/ethyl acetate (5/5)) and evaporation, chlorophthalazines were directly used in the next step.

Formation of the methoxybenzodiazines 17, 24 and 26

A mixture of chlorobenzodiazine (or dichlorobenzodiazine) (1.0 g) in methanol containing dissolved sodium metal (2-4 eq.) was refluxed for 2-48 h. The reaction was monitored by TLC. After cooling, the solvent was removed under reduced pressure. The residue was washed with 10 mL of water and extracted with dichloromethane (3x15 mL). The combined organic extracts were dried over magnesium sulphate and evaporated to give crude methoxybenzodiazines (or dimethoxybenzodiazines).

2-methoxy-3-phenylquinoxaline (17): purification of the crude methoxyquinoxaline by column chromatography (silica, eluent : dichloromethane) afforded 927 mg (95%) of **17** as a white solid, mp 53-54°C; ^{1}H NMR ($CDCl_3$): δ 8.17 (m, 2H, $2H_{Ph}$); 8.13 (dd, J=8.5Hz and 1.3Hz, 1H, H_5); 7.89 (dd, J=7.9Hz and 1.3Hz, 1H, H_8); 7.64 (dd, J=7.9Hz and 7.2Hz, 1H, H_7); 7.54 (m, 4H, $3H_{Ph}$ + H_6); 4.18 (s, 3H, OCH_3);^{15}N NMR ($CDCl_3$) : δ 334 (s, N_4); 265 (s, N_1); ir : ν 1558, 1438, 1331, 1213, 1023, 760, 692, 531 cm^{-1}. Anal. Calcd for $C_{15}H_{12}N_2O$ (236.27): C, 76.25; H, 5.12; N, 11.86. Found: C, 76.27; H, 5.19; N, 11.86.

1-methoxy-4-phenylphthalazine (24): [from 4-phenyl-1(2*H*)-phthalazinone (1g)] purification of the crude methoxyphthalazine by column chromatography (silica, eluent : petroleum ether/ethyl acetate (6/4)) afforded 550 mg (51% in 2 steps) of **24** as a white solid, mp 121-122°C; ^{1}H NMR ($CDCl_3$): δ 8.28 (m, 1H, H_{Benz}); 7.99 (m, 1H, H_{Benz}); 7.82-7.70 (m, 4H, $2H_{Benz}$+$2H_{Ph}$); 7.53 (m, 3H, $3H_{Ph}$); 4.33 (s, 3H, OCH_3); ir : ν 3046, 1539, 1453, 1326, 790, 767, 700, 668 cm^{-1}. Anal. Calcd for $C_{15}H_{12}N_2O$ (236.27): C, 76.25; H, 5.12; N, 11.86. Found: C, 76.18; H, 5.14; N, 11.91.

6-chloro-1,4-dimethoxyphthalazine (26): [from 6-chloro-1,4-dihydroxyphthalazine (1g)] purification of the crude dimethoxyphthalazine by column chromatography (silica, eluent : petroleum ether/ethyl acetate (6/4)) afforded 442 mg (39% in 2 steps) of **26** as a white solid, mp 137-138°C; ^{1}H NMR ($CDCl_3$): δ 8.06 (s, 1H, H_5); 8.04 (d, J=8.7Hz, 1H, H_8); 7.74 (d, J=8.7 Hz, 1H, H_7); 4.18 (s, 6H, $2xOCH_3$); ir : ν 3056, 2949, 1548, 1461, 1374, 1063, 975, 850, 761 cm^{-1}. Anal. Calcd for $C_{10}H_9ClN_2O_2$ (224.65): C, 53.47; H, 4.04; N, 12.47. Found: C, 53.34; H, 4.31; N, 12.30.

6,7-dimethoxy-8-(1-hydroxyethyl)-4-phenylaminoquinazoline (2): metalation of **1** (100 mg, 0.36 mmol) according to the procedure A with *n*-BuLi 1.6 M (5 eq., 1.12 mL), TMPH (5.1 eq., 0.31 mL), t_1 = 2 h, θ_1 = -78°C, followed by reaction with acetaldehyde (2 mL), t_2 = 30 min., θ_2 = -78°C, gave after purification by column chromatography (silica, eluent : ethyl acetate) 105 mg (91%) of **2** as a white solid, mp 204-205°C; ^{1}H NMR ($CDCl_3$): δ 8.56 (s, 1H, H_2); 7.76 (s, 1H, NH); 7.66 (m, 2H, $2H_{Ph}$); 7.50 (1H, OH); 7.39 (m, 2H, $2H_{Ph}$); 7.16 (m, 1H, H_{Ph}); 7.08 (s, 1H, H_5); 5.51 (q, J=6.6 Hz, 1H, CH); 3.97 (s, 3H, OCH_3); 3.89 (s, 3H, OCH_3); 1.64 (d, J=6.6 Hz, 3H, CH_3); ir : ν 3330, 1407, 1267, 1042, 803, 688, 509 cm^{-1}. Anal. Calcd for $C_{18}H_{19}N_3O_3$ (325.37): C, 66.44; H, 5.89; N, 12.91. Found: C, 66.04; H, 6.03; N, 12.59.

Another fraction afforded 9 mg (9%) of starting material.

6,7-dimethoxy-8-(hydroxyphenylmethyl)-4-phenylaminoquinazoline (3): metalation of **1** (100 mg, 0.36 mmol) according to the procedure A with *n*-BuLi 1.6 M (5 eq., 1.12 mL), TMPH (5.1 eq., 0.31 mL), t_1 = 2 h, θ_1 = -78°C, followed by reaction with benzaldehyde (2.2 eq., 80 μL), t_2 = 1 h, θ_2 = -78°C, gave after purification by column chromatography (silica, eluent : petroleum ether/ethyl acetate (5/5)) 117 mg (85%) of **3** as a white solid, mp 231-232°C; ^{1}H NMR ($CDCl_3$): δ 8.56 (s, 1H, H_2); 8.12 (1H, NH); 7.65 (m, 2H, $2H_{Ph}$); 7.53-7.14 (m, 9H, H_5 + $8H_{Ph}$); 7.05 (s, 1H, CH); 6.51 (s, 1H, OH); 3.98 (s, 3H, OCH_3); 3.90 (s, 3H, OCH_3); ir : ν 3317, 2941, 1580, 1528, 1484, 1451, 1409, 1259, 1021, 752 cm^{-1}. Anal. Calcd for $C_{23}H_{21}N_3O_3$ (387.44): C, 71.30; H, 5.46; N, 10.85. Found: C, 71.32; H, 5.35; N, 10.94.

7-chloro-8-(1-hydroxyethyl)-4(3*H*)-quinazolinone (7): metalation of **5** (100 mg, 0.55 mmol) [first reacted with *n*-BuLi 2.5 M (1.1 eq., 0.24 mL)/-78°C/15 min.] according to the procedure A with *n*-BuLi 2.5 M (4 eq., 0.89 mL), TMPH (4.1 eq., 0.39 mL), t_1 = 1 h, θ_1 = -78°C, followed by reaction with acetaldehyde (2 mL), t_2 = 30 min., θ_2 = -78°C, gave after purification by column chromatography (silica, eluent : ethyl acetate) 90 mg (73%) of **7** as a white solid, mp 207-208°C; ^{1}H NMR ($CDCl_3$): δ 11.2 (1H, NH); 8.14 (m, 2H, H_2+H_5); 7.52 (d, J=8.5 Hz, 1H, H_6); 6.70 (q, J=6.4 Hz, 1H, CH); 3.6 (1H, OH); 1.65 (d, J=6.4 Hz, 3H, CH_3); ir : ν 3173, 1677, 1618, 1423, 875, 794 cm^{-1}. Anal. Calcd for $C_{10}H_9ClN_2O_2$ (224.65): C, 53.47; H, 4.04; N, 12.47. Found: C, 53.82; H, 3.87; N, 12.17.

7-chloro-8-(hydroxyphenylmethyl)-4(3*H*)-quinazolinone (8): metalation of **5** (100 mg, 0.55 mmol) [first reacted with *n*-BuLi 2.5 M (1.1 eq., 0.24 mL)/-78°C/15 min.] according to the procedure A with *n*-BuLi 2.5 M (4 eq., 0.89 mL), TMPH (4.1 eq., 0.39 mL), t_1 = 1 h, θ_1 = -78°C, followed by reaction with benzaldehyde (2.2 eq., 0.13 mL), t_2 = 1h30, θ_2 = -78°C, gave after purification by column chromatography (silica, eluent : ethyl acetate) 151 mg (95%) of **8** as a white solid, mp >265°C; ^{1}H NMR ($CDCl_3$): δ 11.4 (1H, NH); 8.24 (s, 1H, H_2); 8.04 (d, J=8.4 Hz, 1H, H_5); 7.55 (d, J=8.4 Hz, 1H, H_6); 7.29 (m, 5H, $5H_{Ph}$); 6.75 (s, 1H, CH); 6.6 (1H, OH); ir :

ν 3344, 2867, 1677, 1621, 1422, 1047, 877, 697 cm^{-1}. Anal. Calcd for $C_{15}H_{11}ClN_2O_2$ (286.72): C, 62.84; H, 3.87; N, 9.77. Found: C, 63.05; H, 3.85; N, 9.58.

6,7-dimethoxy-8-(1-hydroxyethyl)-4(3*H*)-quinazolinone (9): metalation of **6** (100 mg, 0.48 mmol) [first reacted with *n*-BuLi 1.6 M (1.1 eq., 0.33 mL)/-78°C/15 min.] according to the procedure A with *n*-BuLi 1.6 M (4 eq., 1.21 mL), TMPH (4.1 eq., 0.35 mL), t_1 = 2 h, θ_1 = -78°C, followed by reaction with acetaldehyde (2 mL), t_2 = 30 min., θ_2 = -78°C, gave after purification by column chromatography (silica, eluent : ethyl acetate) 60 mg (50%) of **9** as a white solid, mp 180-181°C; ^{1}H NMR ($CDCl_3$): δ 11.1 (1H, NH); 8.03 (s, 1H, H_2); 7.60 (s, 1H, H_5); 6.1 (1H, OH); 5.48 (q, J=6.5 Hz, 1H, CH); 4.01 (s, 3H, OCH_3); 3.98 (s, 3H, OCH_3); 1.62 (d, J=6.5 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) : δ 162.7 (C_4); 152.6, 151.4 ($C_{6/7}$); 142.5 (C_9); 140.7 (C_2); 133.9 (C_8); 119.2 (C_{10}); 105.0 (C_5); 66.06 ($\underline{C}H$); 61.2, 56.1 (2x$O\underline{C}H_3$); 25.8 ($\underline{C}H_3$); ir : ν 3312, 2904, 1667, 1470, 1432, 1041, 798 cm^{-1}. Anal. Calcd for $C_{12}H_{14}N_2O_4$ (250.25): C, 57.59; H, 5.64; N, 11.19. Found: C, 57.68; H, 5.89; N, 11.13.

6,7-dimethoxy-8-(hydroxyphenylmethyl)-4(3*H*)-quinazolinone (10): metalation of **6** (100 mg, 0.48 mmol) [first reacted with *n*-BuLi 1.6 M (1.1 eq., 0.33 mL)/-78°C/15 min.] according to the procedure A with *n*-BuLi 1.6 M (4 eq., 1.21 mL), TMPH (4.1 eq., 0.35 mL), t_1 = 2 h, θ_1 = -78°C, followed by reaction with benzaldehyde (2.2 eq., 0.11 mL), t_2 = 1 h, θ_2 = -78°C, gave after purification by column chromatography (silica, eluent : ethyl acetate) 75 mg (50%) of **10** as a white solid, mp 229-230°C; ^{1}H NMR ($CDCl_3$): δ 11.4 (1H, NH); 7.96 (s, 1H, H_2); 7.66 (s, 1H, H_5); 7.42 (m, 2H, 2H_{Ph}); 7.29 (m, 3H, 3H_{Ph}); 6.70 (d, J=11 Hz, 1H, CH); 6.51 (d, J=11 Hz, 1H, OH); 4.02 (s, 3H, OCH_3); 3.92 (s, 3H, OCH_3); ir : ν 3356, 2869, 1666, 1620, 1471, 1427, 1035, 904, 710 cm^{-1}. Anal. Calcd for $C_{17}H_{16}N_2O_4$ (312.32): C, 65.38; H, 5.16; N, 8.97. Found: C, 65.15; H, 4.89; N, 9.11.

2,2-di(*n*-butyl)-1,2-dihydro-3-methoxyquinoxaline (12): metalation of **11** (100 mg, 0.53 mmol) according to the procedure C with *n*-BuLi 1.6 M (2.2 eq., 0.72 mL), t_1 = 10 min., followed by reaction with acetaldehyde (2 mL), t_2 = 30 min., gave after purification by column chromatography (silica, eluent : petroleum ether/ethyl acetate (8/2)) 127 mg (88%) of **12** as a colorless oil; ^{1}H NMR ($CDCl_3$): δ 7.06 (dd, J=7.6 Hz and 1.4 Hz, 1H, H_{Benz}); 6.89 (td, J=7.6 Hz and 1.4 Hz, 1H, H_{Benz}); 6.66 (td, J=7.6 Hz and 1.2 Hz, 1H, H_{Benz}); 6.49 (dd, J=7.6 Hz and 1.2 Hz, 1H, H_{Benz}); 3.88 (s, 3H, OCH_3); 3.50 (s, 1H, NH); 1.88 (m, 2H, CH_2); 1.55-1.27 (m, 10H, 5xCH_2); 0.90 (m, 6H, 2xCH_3); ^{13}C NMR ($CDCl_3$) : 163.1 (C_3); 136.6, 130 ($C_{9,10}$); 125.7-114.4 ($C_{5,6,7,8}$); 59.3 (C_2); 53.1 ($O\underline{C}H_3$) ; 39.9, 26.2, 22.9 (3x$\underline{C}H_2$) ; 14.0 ($\underline{C}H_3$); ir : ν 2957, 1650, 1495, 1222, 747 cm^{-1}. Anal. Calcd for $C_{17}H_{26}N_2O$ (274.41): C, 74.41; H, 9.55; N, 10.21. Found: C, 74.25; H, 9.60; N, 10.26.

6-chloro-2,3-dimethoxy-5-(1-hydroxyethyl)quinoxaline (14a) and 6-chloro-2,3-dimethoxy-7-(1-hydroxyethyl)quinoxaline (14b): metalation of **13** (100 mg, 0.45 mmol) according to the procedure A with *n*-BuLi 1.6 M (4 eq., 1.11 mL), TMPH (4.1 eq., 0.31 mL), t_1 = 30 min., θ_1 = -78°C, followed by reaction with acetaldehyde (2 mL), t_2 = 30 min., θ_2 = -78°C, gave after purification by column chromatography (silica, eluent : dichloromethane) 97 mg (81%) of **14a** as a white solid, mp 100-101°C; ^{1}H NMR ($CDCl_3$): δ 7.61 (d, J=8.8 Hz, 1H, H_8); 7.45 (d, J=8.8 Hz, 1H, H_7); 5.97 (d, J=11.3 Hz, 1H, OH); 5.59 (sext, J=11.3 and 6.6 Hz, 1H, CH); 4.15 (s, 6H, 2xOCH_3); 1.67 (d, J=6.6 Hz, 3H, CH_3); ir : ν 3403, 1518, 1481, 1406, 1242, 995, 816, 537 cm^{-1}. Anal. Calcd for $C_{12}H_{13}ClN_2O_3$ (268.70): C, 53.64; H, 4.88; N, 10.43. Found: C, 53.57; H, 4.84; N, 10.03.

Another fraction afforded 16 mg (13%) of **14b** as a colorless oil; ^{1}H NMR ($CDCl_3$): δ 7.97 (s, 1H, H_5); 7.75 (s, 1H, H_8); 5.37 (q, J=6.3 Hz, 1H, CH); 4.14 (s, 6H, 2xOCH_3); 2.2 (1H, OH); 1.58 (d, J=6.3 Hz, 3H, CH_3); ir : ν 3278, 1515, 1478, 1382, 1232, 987, 538 cm^{-1}. Anal. Calcd for $C_{12}H_{13}ClN_2O_3$ (268.70): C, 53.64; H, 4.88; N, 10.43. Found: C, 53.58; H, 5.13; N, 10.27.

A third fraction afforded 6 mg (6%) of starting material.

6-chloro-2,3-dimethoxy-5-(hydroxyphenylmethyl)quinoxaline (15a): metalation of **13** (100 mg, 0.45 mmol) according to the procedure A with *n*-BuLi 1.6 M (4 eq., 1.11 mL), TMPH (4.1 eq., 0.31 mL), t_1 = 1 h, θ_1 = -78°C, followed by reaction with benzaldehyde (2.4 eq., 108 μL), t_2 = 1 h, θ_2 = -78°C, gave after purification by column chromatography (silica, eluent : dichloromethane) 125 mg (85%) of **15a** as a pale yellow solid, mp 143-144°C; ^{1}H NMR ($CDCl_3$): δ 7.70 (d, J=8.8 Hz, 1H, H_8); 7.57 (d, J=8.8 Hz, 1H, H_7); 7.44 (m, 2H, $2H_{Ph}$); 7.28 (m, 3H, $3H_{Ph}$); 6.66 (d, J=11.5 Hz, 1H, CH); 6.06 (d, J=11.5 Hz, 1H, OH); 4.14 (s, 3H, OCH_3); 4.00 (s, 3H, OCH_3); ir : ν 3428, 1607, 1515, 1478, 1404, 1237, 983, 546 cm^{-1}. Anal. Calcd for $C_{17}H_{15}ClN_2O_3$ (330.77): C, 61.73; H, 4.57; N, 8.47. Found: C, 62.06; H, 4.43; N, 8.10.

6-chloro-2,3-dimethoxy-5-methylquinoxaline (16a) and 6-chloro-2,3-dimethoxy-5-ethylquinoxaline (16c): metalation of **13** (100 mg, 0.45 mmol) according to the procedure A with *n*-BuLi 1.6 M (4 eq., 1.11 mL), TMPH (4.1 eq., 0.31 mL), t_1 = 1 h, θ_1 = -78°C, followed by reaction with iodomethane (2.4 eq., 67 μL), t_2 = 1 h, θ_2 = -78°C, gave after purification by column chromatography (silica, eluent : petroleum ether/ethyl acetate (7/3)) 114 mg of a mixture of **16a**/**16c**/**13** (proportions : 50/9/41 ; yield : 51%/10%/39%); ^{1}H NMR ($CDCl_3$) of **16a** : δ 7.51 (d, J=8.9 Hz, 1H, H_8); 7.39 (d, J=8.9 Hz, 1H, H_7); 4.12 (s, 6H, $2xOCH_3$); 2.64 (s, 3H, CH_3) ; ^{1}H NMR ($CDCl_3$) of **16c** : δ 7.51 (d, J=8.9 Hz, 1H, H_8); 7.39 (d, J=8.9 Hz, 1H, H_7); 4.12 (s, 6H, $2xOCH_3$); 3.23 (q, J=7.4 Hz, 2H, CH_2); 1.23 (t, J=7.4 Hz, 3H, CH_3).

5-(1-hydroxyethyl)-2-methoxy-3-phenylquinoxaline (18a) and 8-(1-hydroxyethyl)-2-methoxy-3-phenylquinoxaline (18b): metalation of **17** (100 mg, 0.42 mmol) according to the procedure A with *n*-BuLi 1.6 M (4 eq., 1.06 mL), TMPH (4.1 eq., 0.30 mL), t_1 = 30 min., θ_1 =0°C, followed by reaction with acetaldehyde (2 mL), t_2 = 30 min., θ_2 = 0°C, gave after purification by column chromatography (silica, eluent : petroleum ether/ethyl acetate (7/3)) 50 mg (42%) of **18a** as a white solid, mp 90-91°C; ^{1}H NMR ($CDCl_3$): δ 8.12 (m, 2H, $2H_{Ph}$); 7.78 (dd, J=8.3 Hz and 1.4 Hz, 1H, H_8); 7.59 (dd, J= 8.3 Hz and 7.2 Hz, 1H, H_7); 7.49 (m, 4H, $3H_{Ph}+H_6$); 5.54 (quint, J=6.7 Hz, 1H, CH); 5.00 (d, J=6.8 Hz, 1H, OH); 4.18 (s, 3H, OCH_3); 1.75 (d, J=6.6 Hz, 3H, CH_3); ^{15}N NMR ($CDCl_3$) : δ 325 (N_4); 267 (N_1); ir : ν 3362, 1445, 1395, 1331, 1111, 770, 695, 523 cm^{-1}. Anal. Calcd for $C_{17}H_{16}N_2O_2$ (280.33): C, 72.84; H, 5.75; N, 9.99. Found: C, 72.83; H, 5.57; N, 9.81.

Another fraction afforded 9 mg (8%) of **18b** as a yellow oil; ^{1}H NMR ($CDCl_3$): δ 8.10 (m, 2H, $2H_{Ph}$); 8.02 (d, J=7.8 Hz, 1H, H_5); 7.57 (m, 5H, $3H_{Ph}+H_6+H_7$); 5.50 (q, J=6.6 Hz, 1H, CH); 4.4 (1H, OH); 4.16 (s, 3H, OCH_3); 1.74 (d, J=6.6 Hz, 3H, CH_3); ir : ν 3386, 2926, 1634, 1443, 1337, 1076 cm^{-1}. Anal. Calcd for $C_{17}H_{16}N_2O_2$ (280.33): C, 72.84; H, 5.75; N, 9.99. Found: C, 72.77; H, 5.68; N,10.03.

A third fraction afforded 46 mg (46%) of starting material.

5-(hydroxyphenylmethyl)-2-methoxy-3-phenylquinoxaline (19a) and 8-(hydroxyphenylmethyl)-2-methoxy-3-phenylquinoxaline (19b): metalation of **17** (100 mg, 0.42 mmol) according to the procedure A with *n*-BuLi 1.6 M (4 eq., 1.06 mL), TMPH (4.1 eq., 0.30 mL), t_1 = 30 min., θ_1 =0°C, followed by reaction with benzaldehyde (2.2 eq., 95μL), t_2 = 1 h, θ_2 = 0°C, gave after purification by column chromatography (silica, eluent : petroleum ether/ethyl acetate (9/1)) 64 mg (44%) of **19a** as a white solid, mp 100-101°C; ^{1}H NMR ($CDCl_3$): δ 8.03 (m, 2H, $2H_{Ph}$); 7.82 (d, J=8.3 Hz, 1H, H_8); 7.63 (dd, J=8.3 Hz and 7.2 Hz, 1H, H_7); 7.52 (m, 5H, $5H_{Ph}$); 7.40 (d, J=7.2 Hz, 1H, H_6); 7.30 (m, 3H, $3H_{Ph}$); 6.51 (d, J=6 Hz, 1H, CH); 5.51 (d, J=6 Hz, 1H, OH); 4.17 (s, 3H, OCH_3); ^{15}N NMR ($CDCl_3$) : δ 320 (N_4); 267 (N_1); ir : ν 3400, 2947, 1446, 1394, 1338, 1219, 1021, 767, 696, 526 cm^{-1}. Anal. Calcd for $C_{22}H_{18}N_2O_2$ (342.40): C, 77.17; H, 5.30; N, 8.18. Found: C, 77.42; H, 5.05; N, 8.36.

Another fraction afforded 27 mg (19%) of **19b** as a yellow oil; ^{1}H NMR ($CDCl_3$): δ 8.05 (m, 2H, $2H_{Ph}$); 8.01 (dd, J=8.4 Hz and 1.4 Hz, H_5); 7.60 (dd, J=7 Hz and 1.4 Hz, H_7); 7.55 (dd, J=8.4 Hz and 7 Hz, H_6); 7.49 (m, 5H, $5H_{Ph}$); 7.32 (m, 3H, $3H_{Ph}$); 6.49 (d, J=5 Hz, 1H, CH); 4.81 (d, J=5 Hz, 1H, OH); 4.08 (s, 3H, OCH_3); ^{15}N NMR ($CDCl_3$) : δ 336 (N_4); 255 (N_1); ir : ν 3980, 1580, 1382, 1063, 1040, 738, 660, 531 cm^{-1}. Anal. Calcd for $C_{22}H_{18}N_2O_2$ (342.40): C, 77.17; H, 5.30; N, 8.18. Found: C, 77.35; H, 5.17; N, 8.05.

A third fraction afforded 25 mg (25%) of starting material.

2-methoxy-3-phenyl-5-trimethylsilylquinoxaline (20a) and 5,8-di(trimethylsilyl)-2-methoxy-3-phenylquinoxaline (20c): metalation of **17** (100 mg, 0.42 mmol) according to the procedure B with *n*-BuLi 1.6 M (4 eq., 1.06 mL), TMPH (4.1 eq., 0.30 mL), trimethylsilyl chloride (4 eq., 0.22 mL), t = 2 h, θ=0°C, gave after purification by column chromatography (silica, eluent : petroleum ether/ethyl acetate (7/3)) 85 mg (65%) of **20a** as a pale yellow solid, mp 115-116°C; ^{1}H NMR ($CDCl_3$): δ 8.26 (m, 2H, $2H_{Ph}$); 7.85 (dd, J=8.4 Hz and 1.4 Hz, 1H, H_8); 7.71 (dd, J=7.2 Hz and 1.4 Hz, 1H, H_6); 7.62 (dd, J=8.4 Hz and 7.2 Hz, 1H, H_7); 7.48 (m, 3H, $3H_{Ph}$); 4.20 (s, 3H, OCH_3); 0.50 (s, 9H, $Si(CH_3)_3$); ^{15}N NMR ($CDCl_3$) : δ 336 (N_4); 266 (N_1); ir : ν 2949, 1444, 1389, 1248, 1023, 837, 770, 697, 522 cm^{-1}. Anal. Calcd for $C_{18}H_{20}N_2OSi$ (308.45): C,70.09; H, 6.54; N, 9.08. Found: C, 70.15; H, 6.75; N, 8.72.

Another fraction afforded 16 mg (10%) of **20c** as a white solid, mp 135-136°C; ^{1}H NMR ($CDCl_3$): δ 8.22 (m, 2H, $2H_{Ph}$); 7.76 (d, J=6.8 Hz, 1H, H_7); 7.70 (d, J=6.8 Hz, 1H, H_6); 7.50 (m, 3H, $3H_{Ph}$); 4.18 (s, 3H, OCH_3); 0.45 (s, 18H, $2xSi(CH_3)_3$); ^{15}N NMR ($CDCl_3$) : δ 336 (N_4); 268 (N_1). Anal. Calcd for $C_{21}H_{28}N_2OSi_2$ (380.64): C, 66.27; H, 7.41; N, 7.36. Found: C, 66.30; H, 7.78; N, 7.26.

A third fraction afforded 25 mg (25%) of starting material.

1,1-di(*n*-butyl)-1,2-dihydro-4-phenylphthalazine (25): metalation of **24** (100 mg, 0.42 mmol) according to the procedure C with *n*-BuLi 1.6 M (1.2 eq., 0.32 mL), t_1 = 15 min., followed by reaction with acetaldehyde (2 mL), t_2 = 30 min., gave after purification by column chromatography (silica, eluent : petroleum ether/ethyl acetate (5/5)) 62 mg (45%) of **25** as a yellow oil; ^{1}H NMR ($CDCl_3$): δ 7.59 (m, 2H, $2H_{Ph}$); 7.40 (m, 4H, $4H_{Benz}$); 7.26 (m, 3H, $3H_{Ph}$); 1.82 (m, 4H, $2xCH_2$); 1.32 (m, 8H, $4xCH_2$); 0.89 (m, 6H, $2xCH_3$). Anal. Calcd for $C_{22}H_{28}N_2$ (320.48): C, 82.45; H, 8.81; N, 8.74. Found: C, 82.82; H, 8.67; N, 8.83. MS : $[M]^{+\cdot}$, 320; $[M-C_4H_9]^{+\cdot}$, 263.

Another fraction afforded 52 mg (52%) of starting material.

6-chloro-1,4-dimethoxy-7-(1-hydroxyethyl)phthalazine (27) : metalation of **26** (100 mg, 0.45 mmol) according to the procedure C with *n*-BuLi 1.6 M (2.2 eq., 0.61 mL), t_1 = 30 min., followed by reaction with acetaldehyde (2 mL), t_2 = 30 min., gave after purification by column chromatography (silica, eluent : dichloromethane/ethyl acetate (8/2)) 107 mg (89%) of **27** as a white solid, mp 112-113°C; ^{1}H NMR ($CDCl_3$): δ 8.22 (s, 1H, H_5); 7.86 (s, 1H, H_8); 5.36 (q, J=6.3 Hz, 1H, CH); 4.13 (s, 3H, OCH_3); 4.11 (s, 3H, OCH_3); 3.6 (1H, OH); 1.49 (d, J=6.3 Hz, 3H, CH_3); ir : ν 3277, 2949, 1550, 1463, 1358, 1116, 976, 766 cm^{-1}. Anal. Calcd for $C_{12}H_{13}ClN_2O_3$ (268.70): C, 53.64; H, 4.88; N, 10.43. Found: C, 53.51; H, 5.25; N, 10.13.

6-chloro-1,4-dimethoxy-7-(hydroxyphenylmethyl)phthalazine (28) : metalation of **26** (100 mg, 0.45 mmol) according to the procedure C with *n*-BuLi 1.6 M (2.2 eq., 0.61 mL), t_1 = 30 min., followed by reaction with benzaldehyde (2.2 eq., 0.1 mL), t_2 = 1 h, gave after purification by column chromatography (silica, eluent : petroleum ether/ethyl acetate (6/4)) 115 mg (78%) of **28** as a white solid, mp 144-145°C; ^{1}H NMR ($CDCl_3$): δ 8.49 (s, 1H, H_5); 7.97 (s, 1H, H_8); 7.30 (m, 5H, $5H_{Ph}$); 6.29 (s, 1H, CH); 4.17 (s, 3H, OCH_3); 4.14 (s, 3H, OCH_3); 3.6 (1H, OH); ir : ν 3479, 1543, 1367, 1113, 1047, 755, 698 cm^{-1}. Anal. Calcd for $C_{17}H_{15}ClN_2O_3$ (330.77): C, 61.73; H, 4.57; N, 8.47. Found: C, 61.58; H, 4.87; N, 8.20.

6-chloro-1,4-dimethoxy-7-methylphthalazine (29) : metalation of **26** (100 mg, 0.45 mmol) according to the procedure C with *n*-BuLi 1.6 M (2.2 eq., 0.61 mL), t_1 = 30 min., followed by reaction with iodomethane (2.2 eq., 61 μL), t_2 = 1 h, gave after purification by column chromatography (silica, eluent : petroleum ether/ethyl acetate (6/4)) 88 mg of a mixture of **29** and **26** (proportions : 63/37 ; yield : 53%/47%); ^{1}H NMR ($CDCl_3$): δ 8.06 (s, 1H, H_5); 7.94 (s, 1H, H_8); 4.18 (s, 6H, $2xOCH_3$); 2.57 (s, 3H, CH_3).

6-chloro-1,4-dimethoxy-7-iodophthalazine (30) : metalation of **26** (100 mg, 0.45 mmol) according to the procedure C with *n*-BuLi 1.6 M (2.2 eq., 0.61 mL), t_1 = 30 min., followed by reaction with iodine (2 eq., 226 mg), t_2 = 2 h, gave after purification by column chromatography (silica, eluent : petroleum ether/ethyl acetate

(6/4)) 130 mg (83%) of **30** as a white solid, mp 127-128°C; ^1H NMR ($CDCl_3$): δ 8.66 (s, 1H, H_5); 8.17 (s, 1H, H_8); 4.21 (s, 3H, OCH_3); 4.18 (s, 3H, OCH_3); ir : ν 2946, 1531, 1458, 1363, 1117, 890, 762 cm^{-1}. Anal. Calcd for $C_{10}H_8ClIN_2O_2$ (350.54): C, 34.26; H, 2.30; N, 7.99. Found: C, 34.27; H, 2.50; N, 7.78.

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