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Aza-Indolizine with Bridgehead Nitrogen. Metalation, Halogen-Metal Exchange and Directed *Ortho*-Lithiation in the Imidazo[1,2-*a*]pyrazine Series

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Abstract: The *n*-BuLi and lithium 2,2,6,6-tetramethylpiperidine (LTMP) metalation of imidazo[1,2-*a*]pyrazine heterocycles and subsequent quenching with electrophiles is described. Bromine atoms exhibit different behaviours towards lithiation depending on their positions (3 or 6) on the imidazo[1,2-*a*]pyrazine heterocycle. Halogen-metal exchange occurs readily with the bromine on position 3. On the contrary, bromine on position 6 only leads to C-5 substituted derivatives further to an *ortho*-directing effect. © 1998 Elsevier Science Ltd. All rights reserved.

INTRODUCTION

The difficulty in the introduction of a functionality into π-deficient heterocycles by traditional electrophilic substitution renders metalation an attractive alternative.

Since first studies by Gilman[1] and Wittig[2], the direct metalation reaction has evolved into a powerful method for regiospecific preparation and modification of aromatic compounds[3-6]. Although metalation of π-excessive heteroaromatic systems (furan, thiophene) has also been long recognized and explored[7-9], the application of this functionalization strategy to π-deficient heterocycles such as diazines[10-14] and benzodiazines[15] has been recently studied.

The high reactivity of triazines towards nucleophiles makes the metalation of these compounds more difficult than that of most aromatic derivatives which are less sensitive to nucleophilic addition of the base to the azomethine (C=N) bond[16]. This type of addition is clearly a consequence of the strong electron withdrawing effect of the three sp^2 nitrogen atoms that lower the Lowest Unoccupied Molecular Orbital (LUMO) energy[14,15,17]. In the imidazo[1,2-*a*]pyridine series, action of various alkyllithium reagents such as methyl-, *n*-butyl- and phenyllithium followed by reaction with either aldehyde or ketone and acidic hydrolysis led to a monosubstitution on position 3 to yield the expected primary or secondary alcohols[18-20].

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There is no report on the successful metalation of imidazo[1,2-*a*]pyrazine derivatives. In fact, only nucleophilic substitutions on position 8 were observed with either methyllithium (MeLi)[19] or phenyllithium (PhLi)[20]. Alkyllithium, which are strong bases, are also good nucleophiles. On the contrary, less powerful bases such as lithium 2,2,6,6-tetramethylpiperidine (LTMP) or lithium diisopropylamine (LDA) are less prone to nucleophilic addition than alkyllithium[14]. LTMP was selected as lithiating reagent because of its steric hindrance which can prevent this type of addition more than LDA. Actually, yields have been reported to be lower with LDA than with LTMP in the lithiation of 3-chloropyrazine[21], various 3-substituted and 3,6-disubstituted pyridazines[13,22] or 4-chloropyrimidine derivatives[12].

Halogen-metal exchange[23] can also be used to overcome the problem of nucleophilic addition on the azomethine bond. Such reaction, performed at temperatures lower than those of metalation, might prevent nucleophilic attack. Moreover, reaction occurs specifically at the halogenated carbon. In spite of the nucleophilic character of the 3-position in unsubstituted indoles, 3-substituted indoles have been recently prepared by halogen-metal exchange[24]. Halogen-metal exchange has also been applied to pyrimidine derivatives[25,26]. However, this method requires the prior introduction of an halogen atom, e.g. bromine or iodine.

In this paper, we report the functionalization of some imidazo[1,2-*a*]pyrazine derivatives via metalation and halogen-metal exchange. Both reactions allowed us to create new C-C bonds on diverse positions (mostly 3 and/or 5) of the heterocycle after treatment of the lithio intermediates with electrophiles such as aldehydic or halogenated compounds. The different behaviours towards lithiation of the bromine atoms on positions 3 and 6 provided a good tool for a regioselective substitution of the imidazo[1,2-*a*]pyrazines.

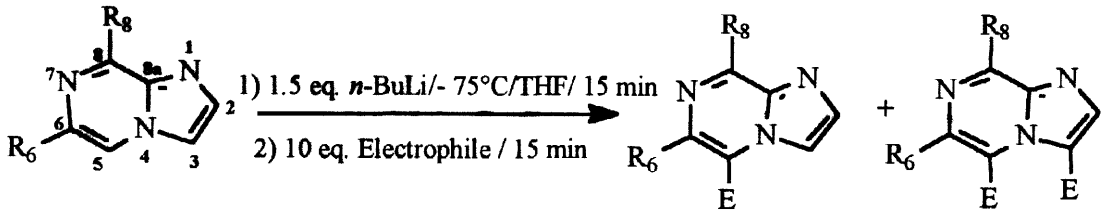
RESULTS

Metalation of imidazo[1,2-a]pyrazines.

- with n-BuLi

Lithiations of imidazo[1,2-*a*]pyrazine **1**, 8-methoxyimidazo[1,2-*a*]pyrazine **2** and 6-bromo-8-methoxyimidazo[1,2-*a*]pyrazine **3** were performed in dry THF by treatment with 1.5 equivalents of *n*-BuLi at -75 °C for 15 min followed by reaction with D_2O (for **1**) and propionaldehyde (for **2** and **3**) as electrophiles (Scheme 1, Table 1). When the reaction was quenched with D_2O, no deuterium incorporation was observed. No reaction also occured with **2**. In both cases, starting materials were recovered. Only the 6-bromo derivative **3** reacted to yield the mono- and disubstituted imidazo[1,2-*a*]pyrazines **4** and **5** in 60% and 20% yields, respectively, besides unchanged material.

Scheme 1



1 R_6=H, R_8=H — no reaction

2 R_6=H, R_8=OMe — no reaction

3 R_6=Br, R_8=OMe — **4** (60%) + **5** (20%)

Table 1. Metalation with *n*-BuLi

Starting materials	Electrophile	E	Position of ring substitution	
			C-5	C-3 and C-5
1	D_2O	D	no reaction	
2	CH_3CH_2CHO	CH_3CH_2CHOH	no reaction	
3	CH_3CH_2CHO	CH_3CH_2CHOH	60 % (4)	20 % (5)

Mass spectrometry indicated the presence of a bromine atom in both compounds. Assignments of the ^1H and ^{13}C NMR spectra were achieved according to previously published data[27]. For the major product **4**, two doublets at δ 7.41 and 8.21 were found to be coupled with a small coupling constant, J = 1 Hz, characteristic of an H-2,H-3 coupling[27]. Moreover, the ^1H-^1H COSY spectrum exhibited correlations between aromatic protons H-2 and H-3. These results unambiguously proved that the site of substitution was not on C-2 or C-3. The hydrogenolysis of the carbon-bromine bond allowed us to determine the position of substitution. Actually, substitution might have occurred either on C-5, due to an *ortho*-directing effect of bromine, or on C-6, as a result of an halogen scrambling[28,29]. Compound **4** was hydrogenated at atmospheric-pressure in a sloping-Manifold hydrogenator with Pd/C (5%) as catalyst and dry EtOH as solvent[30] to yield compound **4a**. A ^1H NMR ROESY study performed on **4a** showed that aliphatic CH and CH_2 protons of the electrophilic moiety correlated with two aromatic protons, H-3 and H-6. Such correlation can only be observed if the substitution position is on C-5, in accord with an ortho-directing effect of the bromine on position 6. NMR data and mass spectrometry indicated that **5** was disubstituted with two secondary alcohols. The positions of the aliphatic chains were determined to be 3 and 5 after hydrogenolysis of **5** as already

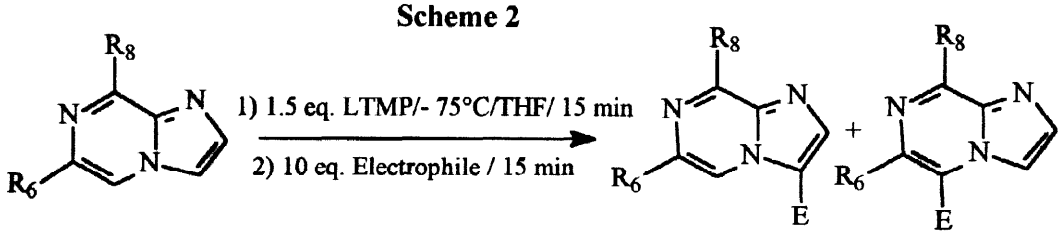
described. The resulting compound **5a** was identified by ^{1}H NMR indicating that both aromatic protons were *ortho* to the side chains.

Thus, metalation of 6-bromo-8-methoxyimidazo[1,2-*a*]pyrazine **3** with *n*-BuLi as metalating reagent, afforded mono- and disubstituted compounds at positions 5 and 3,5.

- with LTMP:

Imidazo[1,2-*a*]pyrazine **1**, 8-methoxyimidazo[1,2-*a*]pyrazine **2** and 6-bromo-8-methoxyimidazo[1,2-*a*]pyrazine **3** were treated in anhydrous THF with 1.5 equivalents of the nonnucleophilic lithiating agent LTMP at -75°C for 15 min followed by reaction with propionaldehyde (Scheme 2, Table 2).

Scheme 2



1 R_6=H, R_8=H	**6** (15%)	**7** (15%)
2 R_6=H, R_8=OMe	no reaction	
3 R_6=Br, R_8=OMe	-	**4** (20%)

Table 2. Metalation with LTMP

Starting materials	Electrophile	E	Position of ring substitution C-3	C-5
1	CH_3CH_2CHO	CH_3CH_2CHOH	15% (6)	15% (7)
2	CH_3CH_2CHO	CH_3CH_2CHOH	no reaction	
3	CH_3CH_2CHO	CH_3CH_2CHOH	-	20% (4)

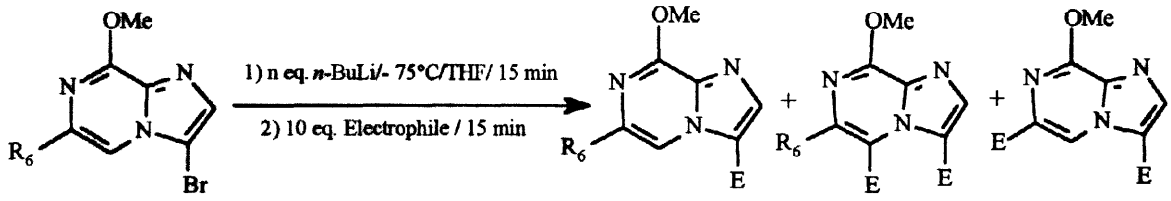
A set of two inseparable monosubstituted compounds **6** and **7** in equal amounts (15% yield each) was obtained besides unchanged material with the unsubstituted imidazo[1,2-*a*]pyrazine **1.** ^{1}H NMR data of the **6/7** mixture indicated that monosubstitution at C-3 or C-5 occurred. No reaction occurred with **2**. In this case, starting material was recovered. Lithiation of **3** with LTMP led to one secondary alcohol in 30% yield besides starting material. The substitution on the C-5 position was established by mass spectrometry and ^{1}H NMR. This compound was found to be identical to compound **4** already obtained from the lithiation with *n*-BuLi.

In summary, lithiation with the nonnucleophilic base LTMP afforded monosubstituted products, on positions 3 and 5 with the unsubstituted imidazo[1,2-*a*]pyrazine **1** and only on position 5, in presence of the *ortho*-directing effect of a bromine atom at position 6. However, this lithiating reagent is not regioselective even at low temperature, except with **3** at C-5, and only gives poor yields. The use of LTMP is not necessary, since, contrary to results with MeLi[19] or PhLi[20], *n*-BuLi did not lead to any nucleophilic substitution or addition.

Halogen-Metal Exchange of 3-bromoimidazo[1,2-a]pyrazines.

Compounds **10** and **5a** on one hand, **11** to **19**, on the other hand were formed after halogen-metal exchange on 3-bromo-8-methoxy- and 3,6-dibromo-8-methoxyimidazo[1,2-*a*]pyrazine **8** and **9**, respectively. The lithio species generated with 1.5 or 2 equivalents of *n*-BuLi at -75°C for 15 min were trapped *in situ*, by reaction with propionaldehyde for **8** or various electrophiles for **9** (Scheme 3, Table 3).

Scheme 3



8 R_6=H
9 R_6=Br

10 **12,14,16,18,19**

5a **5,11,13,17**

- **15**

Table 3. Halogen-Metal exchange and Lithiation with *n*-BuLi

Starting materials	Electrophile	E	n (eq.)	T (°C)	Position of ring substitution C-3	C-3 and C-5	C-3 and C-6
8	CH_3CH_2CHO	CH_3CH_2CHOH	1.5	- 75	60% (**10**)	20% (**5a**)	-
9	HCHO	CH_2OH	1.5	- 75	40% (**12**)	40% (**13**)	-
9	CH_3CH_2CHO	CH_3CH_2CHOH	1.5	- 75	20% (**14**)	40% (**5**)	15% (**15**)
9	$(CH_3)_2CHCHO$	$(CH_3)_2CHCHOH$	1.5	- 75	95% (**16**)	5% (**17**)	-
9	$(CH_3)_2CHCH_2CHO$	$(CH_3)_2CHCH_2CHOH$	1.5	- 75	quantitative (**18**)	-	-
9	$(CH_3)_2CHCH_2Br$	$(CH_3)_2CHCH_2$	1.5	- 75		no substitution	
			1.5	0	quantitative (**19**)	-	-
9	DCl	D	2.0	- 75	-	80 % (**11**)	-

Lithiation of **8** led to a set of two separable compounds, a monosubstituted **10**, and a disubstituted imidazo[1,2-*a*]pyrazine in 60% and 20% yield, respectively. The dialcohol obtained was found to be similar to **5a**. The dibromo derivative **9** was converted exclusively in the 3,5-dideutero derivative **11** after reaction with DCl as the electrophile. Quenching the lithiated species formed by lithiation of **9** with various electrophiles afforded the monosubstituted derivatives **12**, **14**, **16**, in 40%, 20%, 95% yields respectively and **18** and **19** quantitatively. Disubstituted products **13**, **5**, **15** and **17** were also isolated besides **12**, **14** and **16**.

Positions of ring substitution were determined for all derivatives after hydrogenolysis followed by ^{1}H NMR experiment on the resulting compounds. The ^{1}H NMR spectra of mono- and disubstituted derivatives unambiguously indicated positions 3 and 3,5 as positions of substitution, respectively.

A small amount of a disubstituted non-halogenated imidazo[1,2-*a*]pyrazine derivative **15** was obtained besides the mono- and 3,5-disubstituted compounds **14** and **5**. The ^{1}H-^{1}H COSY spectrum showed correlations between both aromatic protons and aliphatic CH protons. These data gave positions 3 and 6 as positions of substitution for **15**.

When isobutyl bromide was used as the electrophile at low temperature (-75°C), no substitution occurred and compound **3** was formed quantitatively by hydrogen exchange during acidic hydrolysis. However, substitution reaction was successful when the electrophile was added at 0°C.

Thus, lithiation on **8** and **9** with *n*-BuLi afforded mono- and disubstituted products at positions 3 and 3,5 respectively. Halogen-metal exchange occurred at the bromine on position 3. Interestingly, halogen-metal exchange of both bromine atoms (at C-3 and C-6) were only observed in one case. Indeed, atoms of bromine at position 3 and 6 appear to behave in very different manners in such conditions of reaction.

DISCUSSION

Despite previous negative results with diverse alkyllithiums and aryllithiums such as MeLi[19] and PhLi[20], lithiation of the unsubstituted imidazo[1,2-*a*]pyrazine successfully occurred with *n*-BuLi and the non-nucleophilic base LTMP. The lithio intermediates were quenched with electrophiles to yield 3- and 5-substituted products. Since no nucleophilic substitution was observed with *n*-BuLi, the use of less reactive reagents in our heterocyclic system, such as LTMP, are not necessary and can be discarded. Furthermore, LTMP is not regioselective and gives low yields.

The reaction with *n*-BuLi generally led to a mixture of compounds with an amount of disubstituted compounds. The classical addition of the *n*-BuLi to the imidazopyrazine solution allowed the reaction mixture to reach an equilibrium between various lithiated species. To determine the formation of a dilithio species, the reaction was performed with an excess of *n*-BuLi (2.0 equivalents) and DCl as the electrophile. Interestingly, under these conditions, the 3,5-disubstituted compound was obtained as the sole product. This

result unambigously proved the presence of a dilithio derivative in the reaction mixture. Such derivatives have been previously suggested as intermediates in heterocyclic series[10,31].

Depending on their positions on the imidazo[1,2-*a*]pyrazine heterocycle, bromine atoms exhibited very different behaviours towards *n*-BuLi : *ortho*-directing efficiency of the bromine on position 6 and exchange with lithium for the bromine on position 3. For further preparative purposes, the bromine-lithium exchange reaction offers the great advantage of the obtention of very high, indeed even quantitative, yields, providing a very good route to 3-substituted imidazo[1,2-*a*]pyrazines. Furthermore, it was possible to rationalize the difference of regioselectivity observed with the nature of the electrophile. Regioselectivity in the halogen-metal exchange reaction of 3,6-dibromo-8-methoxyimidazo[1,2-*a*]pyrazine greatly depended on the nature of the added electrophile. The more sterically hindered the electrophile was, the more regioselective at the halogenated carbon 3 the reaction was. From the different results obtained after reaction of *n*-BuLi on the 3,6-dibromo-8-methoxyimidazo[1,2-*a*]pyrazine **9**, it can be stated that the main intermediate in the reaction mixture is the dilithio derivative. Small electrophiles can directly attack the two sites on position 3 and 5, leading to disubstituted derivatives. On the contrary, when electrophiles are larger, they first attack position 3 and this first attack impedes or even blocks any further reaction on position 5.

In conclusion, lithiation with *n*-BuLi as metalating reagent, afforded mono- and disubstituted compounds on positions 5 and 3,5 according to an *ortho*-directing effect of the bromine on position 6. In our conditions, no nucleophilic attack by *n*-BuLi occurred. With bromine substituted heterocycles, reactivity clearly depends on the position of the halogen and exhibits high regioselectivity. Bromine-lithium exchange selectively occurs on position 3, even when position 6 is halogenated, whereas a bromine atom on position 6 mainly exhibits an *ortho*-directing effect. No halogen scrambling was observed in this series under our conditions of reaction. Lithiation of the unsubstituted imidazo[1,2-*a*]pyrazine can be achieved with lithium alkylamides such as LTMP. However, this reagent provides poor yields and regioselectivity.

EXPERIMENTAL

All melting points, determined on a Köfler hot plate apparatus, were uncorrected. Thin Layer Chromatography (TLC) was performed on silica gel SIL G/UV_{254} (Macherey-Nagel) plates and spots were visualized by UV. ^{1}H and ^{13}C NMR spectra were recorded on a Brucker AC 100 or AC 360 spectrometer. Mass spectrometry was realized on a LKB 2091 spectrometer at 15 eV [(θ_{source}): 180°C]. Compounds were purified by column chromatography on silica gel (CH_2Cl_2).

THF was distilled from benzophenone/sodium and used immediately.

Compounds **1-3**, **8**, **9** were synthesized as previously described[32]. Commercial aldehydes were distilled before the reaction. The 1.6 M commercial solution of *n*-butyl- lithium in hexane was titrated according to

the procedure of Watson et al.[33]. LTMP was prepared by reaction of 2,2,6,6-tetramethylpiperidine (TMPH) (0.40 mL, 2.25 mmol) in dry THF (10 mL) and *n*-butyllithium (1.40 mL, 1.6 M, 2.25 mmol) at -30°C and then at 0°C for 30 min. TMPH was distilled from CaH_2 and stored under a dry nitrogen atmosphere.

All reactions involving air-sensitive reagents were performed using syringe-septum cap techniques in oven dried glassware under dry nitrogen atmosphere.

General Procedure A : *n*-BuLi. To a solution or a suspension of imidazo[1,2-*a*]pyrazine derivative (1.50 mmol) in dry THF (10 mL), *n*-BuLi (1.6 M in hexane, 1.40 mL, 2.25 mmol) was added slowly at -75°C under a flow of dry nitrogen. The resulting purple or brown solution was stirred for 15 min at -75°C. The appropiate aldehyde (30 mmol) was then added slowly and the resulting solution was stirred at -75°C for further 15 min before hydrolysis by 10 mL of HCl/EtOH/THF (1:1:1). The solution was warmed to r.t., basified with a satured aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2.

General Procedure B : LTMP. A solution of imidazo[1,2-*a*]pyrazine derivative (1.50 mmol) in dry THF (10 mL) was slowly added to the cold (-75°C) solution of LTMP (cf above). The mixture was stirred for 15 min at -75°C before addition of the appropiate aldehyde (30 mmol). Stirring was maintained for 15 min at -75°C before hydrolysis (-75°C) by 10 mL of HCl/EtOH/THF (1:1:1). The solution was gently warmed to r.t., basified with a saturated solution of $NaHCO_3$ and extracted by CH_2Cl_2.

General Procedure of Hydrogenolysis. To a solution of imidazo[1,2-*a*]pyrazine derivative (1.50 mmol) in dry EtOH (20 mL) was added Pd/C 5% (50 mg) and the mixture was shaken at atmospheric-pressure in a sloping-Manifold hydrogenation apparatus during 6h. The catalyst was removed by filtration, and the filtrate was concentrated in vacuo to give dehalogenated compound in 90% yield.

Theoretical calculations. LUMO calculations were obtained by semi-empirical method (MOPAC 6.0 with AM1 hamiltonian)[34] on a HP 730 cluster of workstation using the Molecular Advanced Design Software[34].

6-Bromo-5-(hydroxypropyl)-8-methoxyimidazo[1,2-*a*]pyrazine (4). General procedure A and B were applied to 340 mg of **3** and propionaldehyde to obtain **4** in 60% and 20% yield, respectively : oil; R_f 0.63 (eluent, CH_2Cl_2/methanol (9/1)) ^1H NMR ($CDCl_3$) δ 8.35 (d, J = 1 Hz, 1 H), 7.47 (d, J = 1Hz, 1 H), 5.46 (t, 1 H), 4.07 (s, 3 H), 2.05 (m, 2 H); 1.10 (t, 3 H); MS (*m/z*) 285 ($M^{+\cdot}$), 270, 254. Calcd for $C_{10}H_{12}BrN_3O_2$: C, 42.10; H, 4.24; N, 14.74. Found: C, 41.95; H, 4.21; N, 14.85.

5-(Hydroxypropyl)-8-methoxyimidazo[1,2-*a*]pyrazine (4a). General procedure of hydrogenolysis was applied to 100 mg of **4** to obtain **4a** : mp 168-170 °C; R_f 0.60 (eluent, CH_2Cl_2/methanol (9/1)) ^1H NMR ($CDCl_3$) δ 8.21 (d, J = 1 Hz, 1 H), 7.63 (d, J = 1Hz, 1 H), 7.35 (s, 1 H) 5.43 (t, 1 H), 4.03 (s, 3 H), 1.98 (m,

2 H); 1.07 (t, 3 H); MS (*m/z*) 207 ($M^{+\cdot}$), 178, 139. Anal. Calcd for $C_{10}H_{13}BrN_3O_2$: C, 57.94; H, 6.33; N, 20.28. Found: C, 58.01; H, 6.37; N, 20.22.

6-Bromo-3,5-(dihydroxypropyl)-8-methoxyimidazo[1,2-*a*]pyrazine (5). General procedure A was applied to 340 mg of **3** and 230 mg of **9** and propionaldehyde to provide **5** after cristalization in CH_2Cl_2 in 20% and 40% yield, respectively : mp 174-176 °C; R_f 0.60 (eluent, CH_2Cl_2/methanol (9/1)); ^1H NMR (DMSO) δ 7.55 (s, 1 H), 5.61 (t, 1 H), 5.23 (t, 1 H), 3.99 (s, 3 H), 2.02 (m, 4 H), 1.01 (t, 6 H); MS (*m/z*) 343 ($M^{+\cdot}$), 325, 296. Anal. Calcd for $C_{13}H_{18}BrN_3O_3$: C, 45.47; H, 5.29; N, 12.25. Found: C, 45.36; H, 5.38; N, 12.18.

3,5-(Dihydroxypropyl)-8-methoxyimidazo[1,2-*a*]pyrazine (5a). Compound **5a** was obtained from 100 mg of **5** by hydrogenolysis (yield : 90%). **5a** was also obtained directly through general procedure A besides compound **10** (see infra): mp 180-182 °C; R_f 0.42 (eluent, CH_2Cl_2/methanol (9/1)); ^1H NMR (DMSO) δ 7.65 (s, 1 H), 7.49 (s, 1 H), 5.13 (t, 1 H), 5.02 (t, 1 H), 4.02 (s, 3 H), 1.93 (m, 4 H), 1.02 (t, 6 H); MS (*m/z*) 265 ($M^{+\cdot}$), 247, 218. Anal. Calcd for $C_{13}H_{19}N_3O_3$: C, 58.85; H, 7.22; N, 15.84. Found: C, 58.92; H, 7.27; N, 15.79.

3-(Hydroxypropyl)imidazo[1,2-*a*]pyrazine (6) and 5-(hydroxypropyl)imidazo[1,2-*a*]pyrazine (7). General procedure B was applied to 180 mg of **1** and propionaldehyde to give a mixture of **6** and **7** in 15 % yield each which were found to be inseparable either by column chromatography or cristallization : oil; R_f 0.23 (eluent, CH_2Cl_2/methanol (9/1)); **6**: ^1H NMR ($CDCl_3$) δ 8.73 (d, J = 1.5 Hz, 1 H), 8.24 (dd, J_1 = 1.5 Hz, J_2= 5 Hz, 1 H), 7.64 (d, J = 5 Hz, 1 H), 7.56 (s, 1 H); **7**: ^1H NMR ($CDCl_3$) δ 8.66 (d, J = 1 Hz, 1 H), 7.92 (d, J = 1 Hz, 1 H), 7.56 (d, J = 1 Hz, 1 H), 7.23 (d, J = 1 Hz, 1 H); MS (*m/z*) 177 ($M^{+\cdot}$), 148, 118.

3-(Hydroxypropyl)-8-methoxyimidazo[1,2-*a*]pyrazine (10). General procedure A was applied to 170 mg of **8** and propionaldehyde to afford **5a** and **10** in 20 % and 60 % yield, respectively: oil; R_f 0.43 (eluent, CH_2Cl_2/methanol (9/1)); ^1H NMR ($CDCl_3$) δ 8.03 (d, J = 5 Hz, 1 H), 7.51 (s, 1 H), 7.36 (d, J = 5 Hz, 1 H), 4.91 (t, 1 H), 4.07 (s, 3 H), 2.05 (m, 2 H), 1.08 (t, 3 H); MS (*m/z*) 207 ($M^{+\cdot}$), 178, 139. Anal. Calcd for $C_{10}H_{13}N_3O_2$: C, 57.94; H, 6.33; N, 20.28. Found: C, 57.97; H, 6.31; N, 20.17.

6-Bromo-3,5-dideutero-8-methoxymethoxyimidazo[1,2-*a*]pyrazine (11). General procedure A with the use of 3.00 mmol of *n*-BuLi was applied to 460 mg of **9** and DCl to afford **11** in 80 % yield: R_f 0.40 (eluent, CH_2Cl_2/methanol (9/1)); ^1H NMR ($CDCl_3$) δ 7.62 (s, 1 H), 4.14 (s, 3 H); MS (*m/z*) 229. Anal. Calcd for $C_7H_4D_2N_3OBr$: C, 37.01; H, 2.66; N, 18.51. Found: C, 36.97; H, 2.72; N, 18.56.

6-Bromo-3-(hydroxymethyl)-8-methoxyimidazo[1,2-*a*]pyrazine (12) and 6-bromo-3,5-(dihydroxymethyl)-8-methoxyimidazo[1,2-*a*]pyrazine (13). General procedure A was applied to 230 mg of **9** and paraformaldehyde in dry THF (10 mL) to give a mixture of **12** and **13** which were separated by column chromatography on silica gel (eluant, CH_2Cl_2/methanol (9/1)); **12** (40 % yield): mp 200-202 °C; R_f 0.40 (eluent, CH_2Cl_2/methanol (9/1)); ^{1}H NMR ($CDCl_3$) δ 8.06 (s, 1 H), 7.53 (s, 1 H), 4.95 (s, 2 H) 4.18 (s, 3 H); MS (*m/z*) 258 ($M^{+\cdot}$), 243, 227. Anal. Calcd for $C_8H_8BrN_3O_2$: C, 37.36; H, 3.14; N, 16.35. Found: C, 37.27; H, 3.09; N, 16.43. **13** (40 % yield): mp >260 °C; R_f 0.35 (eluent, CH_2Cl_2/methanol (9/1)); ^{1}H NMR (DMSO) δ 7.52 (s, 1 H), 4.93 (s, 2 H), 4.91 (s, 2 H), 4.13 (s, 3 H); MS (*m/z*) 287 ($M^{+\cdot}$), 272, 256. Anal. Calcd for $C_9H_{10}BrN_3O_3$: C, 37.63; H, 3.51; N, 14.64. Found: C, 37.51; H, 3.42; N, 14.58.

6-Bromo-3-(hydroxypropyl)-8-methoxyimidazo[1,2-*a*]pyrazine (14) and 3,6-(dihydroxypropyl)-8-methoxyimidazo[1,2-*a*]pyrazine (15). General procedure A was applied to 230 mg of **9** and propionaldehyde to afford a mixture of compounds **5** (40 %), **14** (20 %) and **15** (15 %) which were separated by column chromatography on silica gel (eluant, CH_2Cl_2/methanol (9/1)). **14**: oil; R_f 0.63 (eluent, CH_2Cl_2/methanol (9/1)); ^{1}H NMR ($CDCl_3$) δ 8.22 (s, 1 H), 7.49 (s, 1 H), 5.39 (t, 3 H), 4.08 (s, 3 H), 2.01 (m, 2 H), 1.00 (t, 3 H); MS (*m/z*) 285 ($M^{+\cdot}$), 270, 254. Anal. Calcd for $C_{10}H_{12}BrN_3O_2$: C, 42.10; H, 4.24; N, 14.74. Found: C, 41.98; H, 4.18; N, 14.85. **15**: mp 180-182 °C; R_f 0.50 (eluent, CH_2Cl_2/methanol (9/1)); ^{1}H NMR ($CDCl_3$) δ 7.90 (s, 1 H), 7.48 (s, 1 H), 4.90 (t, 1 H), 4.52 (t, 1 H), 3.99 (s, 3 H), 2.05 (m, 4 H), 1.04 (t, 6 H); MS (*m/z*) 265 ($M^{+\cdot}$), 236, 218. Anal. Calcd for $C_{13}H_{19}N_3O_3$: C, 58.85; H, 7.22; N, 15.84. Found: C, 58.69; H, 7.17; N, 15.97.

6-Bromo-3-(hydroxyisobutyl)-8-methoxyimidazo[1,2-*a*]pyrazine (16) and 6-bromo-3,5-(dihydroxyisobutyl)-8-methoxyimidazo[1,2-*a*]pyrazine (17). General procedure A was applied to 230 mg of **9** and isobutyraldehyde and afforded a mixture of compounds **16** and **17** which were separated by column chromatography on silica gel (eluant, CH_2Cl_2/methanol (9/1)). **16** (95 % yield): mp 188-190 °C; R_f 0.60 (eluent, CH_2Cl_2/methanol (9/1)); ^{1}H NMR ($CDCl_3$) δ 8.23 (s, 1 H), 7.53 (s, 1 H), 5.09 (d, J = 10Hz, 1 H), 4.05 (s, 3 H), 2.41 (m, J = 10Hz, 1 H), 1.21 (d, J = 6Hz, 3 H), 0.80 (d, J = 6Hz, 3 H); MS (*m/z*) 299 ($M^{+\cdot}$), 256, 227. Anal. Calcd for $C_{11}H_{14}BrN_3O_2$: C, 44.02; H, 4.70; N, 14.00. Found: C, 44.17; H, 4.72; N, 14.12. **17** (5 % yield). mp 195-197°C; R_f 0.53 (eluent, CH_2Cl_2/methanol (9/1)); ^{1}H NMR ($CDCl_3$) δ 7.53 (s, 1 H), 5.07 (d, 1 H, J = 10Hz), 4.95 (d, 1 H, J = 10Hz), 4.03 (s, 3 H), 2.38 (m, 2 H), 1.22 (d, 6 H), 0.83 (d, 6 H); MS (*m/z*) 371 ($M^{+\cdot}$), 328, 285. Anal. Calcd for $C_{15}H_{22}BrN_3O_3$: C, 48.40; H, 5.96; N, 11.29. Found: C, 48.53; H, 6.04; N, 11.40.

6-Bromo-3-(hydroxyisopropyl)-8-methoxyimidazo[1,2-*a*]pyrazine (18). General procedure A was applied to 230 mg of **9** and isovaleraldehyde. Compound 17 was formed quantitatively: mp 170-172 °C; R_f 0.44 (eluent, CH_2Cl_2/methanol (9/1)); ^1H NMR ($CDCl_3$) δ 8.27 (s, 1 H), 7.46 (s, 1 H), 5.53 (t, 1 H), 4.10 (s, 3 H), 1.95 (m, 2 H), 1.56 (m, 1 H), 1.05 (d, 3 H), 1.02 (d, 3 H); MS (*m/z*) 313 ($M^{+\cdot}$), 256, 227. Anal. Calcd for $C_{12}H_{16}BrN_3O_2$: C, 45.88; H, 5.13; N, 13.37. Found: C, 46.00; H, 5.22; N, 13.45.

6-Bromo-3-(isobutyl)-8-methoxyimidazo[1,2-*a*]pyrazine (19). General procedure A was applied to 230 mg of **9** and isobutyl bromide. After addition of the electrophile, the temperature was warmed up to rt. After 15 min, the reaction mixture was cooled to -75°C before hydrolysis by 10 mL of HCl/EtOH/THF. The solution was warmed up to rt, basified with a satured aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2. No trace of the started product was detected in U.V. Compound **19** was formed quantitatively: mp 158-160 °C; R_f 0.10 (eluent, CH_2Cl_2/methanol (9/1)); ^1H NMR ($CDCl_3$) δ 7.92 (s, 1 H), 7.61 (s, 1 H), 4.17 (s, 3 H), 2.24 (m, 1 H), 1.65 (m, 2 H) 1.02 (d, 6 H); MS (*m/z*) 283 ($M^{+\cdot}$), 240, 227. Anal. Calcd for $C_{11}H_{14}BrN_3O$: C, 46.50; H, 4.97; N, 14.79. Found: C, 46.54; H, 5.02; N, 14.91.

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