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First Metallation of Iodo Diazines. Iodo and Nitrogen Directed Metallations. Diazines XXII.

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This paper is dedicated to Professor Alan R. Katrisky on the occasion of his 70th birthday.

Abstract: Lithiation of iodopyrazine and 4-iodo-2-methylthiopyrimidine followed by reaction with various electrophiles was successfully achieved and was used to synthesize new pyrazine and pyrimidine derivatives. Iodo and nitrogen directed metallations were observed.

Metallation of arylfluorides and chlorides has been previously reported in both aromatic and heteroaromatic systems.[1,2] The scope of this methodology is currently well defined.[1,3] Compared to the metallation of chloro and fluoro aromatics, few metallations have been done with bromine or iodine. In particular the metallation of bromobenzene[4] and bromopyridines[5] has been carried out, the "halogen-dance" phenomenon has been discovered,[4,6] and this reaction has then been used for synthetic purposes.[6,7]

The first iodo-directed metallation of aromatics was described with iodothiophene[8] and iodoisothiazole.[9] Metallation of 2-iodothiophene performed either with a complex phenyllithium/TMEDA[8] or LDA[10] mainly led to a regioselective metallation at the C_5 position. Attempts to metallate 3-iodopyridine performed by Gribble[11] with LDA as the metallating agent were unsuccessful, this failure has been assigned to the instability of 3-iodo-4-lithiopyridine. More recently the metallation of iodopyridines was successfully achieved,[12,13] but authors emphasized that the metallation of iodopyridines proved to be feasible only on the condition that the pyridine nucleus bears an inductive electronwithdrawing substituent (chloro, fluoro, *N,N*-diisopropylcarboxamido). In these cases, lithiation is ortho-directed by the iodo group which subsequently ortho migrates very fast to give a more stabilized iodolithiopyridine. These results indicated that the iodo group is an inefficient ortho-directing group which cannot stabilize alone the lithio derivative.

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To our knowledge, no iodo-directed metallation of diazines has been described. This provides a promising challenge since in the diazine series, iodine displays a high reactivity in such useful reactions as halogen-lithium exchange,[14] cross-coupling[15] and trifluoromethylation,[16] but the metallation could be difficult to carry out. It should be noted that in diazines the electron deficiency of the nucleus increases the acidity of the hydrogens, allowing deprotonation without directing metallation group.[17] In these cases, no stabilization of the lithio derivative occurred, making the latter more subject to side reactions, and metallation must be achieved with short reaction times (5 min). The regioselectivity observed was exclusively ortho to nitrogen ring.

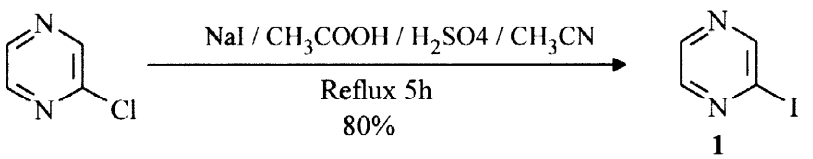
It will be interesting and exciting to see if the metallation of iodopyrazine and iodopyrimidine is possible and what directs the regioselectivity between iodo group and nitrogen ring. Following our investigation in the field of the functionalization of diazines *via* metallation, we wish to report here the synthesis and first lithiation of iodopyrazine **1** and 4-iodo-2-methylthiopyrimidine **2**.

Syntheses of iodopyrazine **1** and 4-iodo-2-methylthiopyrimidine **2** have been previously described by the nucleophilic substitution of corresponding chloro derivatives. So, starting from chloropyrazine, iodopyrazine **1** was obtained with moderate yield (40%),[18,19] and reaction between hydroiodic acid and 4-chloro-2-methylthiopyrimidine led to **2** (76%).[19]

RESULTS

By refluxing chloropyrazine and sodium iodide in a mixture of acetic acid, sulfuric acid and acetonitrile we have highly improved the yield of **1** from 40%[18,19] to 80% (Scheme 1).

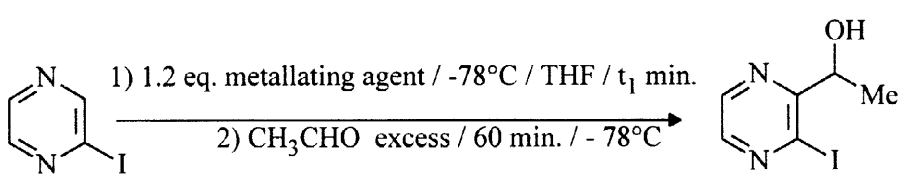
Scheme 1



1

In order to determine the most efficient conditions for the metallation of **1**, various metallating agents such as lithium diisopropylamide (LDA), lithium 2,2,6,6,-tetramethylpiperidide (LTMP), or lithium N,N-*tert*-butyl(1-isopropyl)pentylamide (LB1) have been used and various reaction times have been tested with acetaldehyde as the electrophile (Scheme 2, Table 1).

Scheme 2



1 **3**

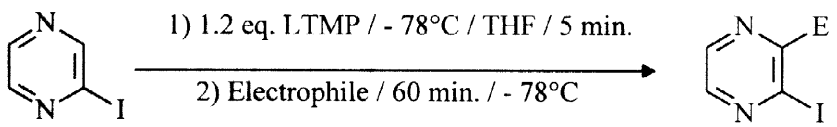
Table 1.- *Metallation of iodopyrazine 1 and reaction with acetaldehyde*

Entry	Metallating agent	t_1 min.	3	Starting material 1
1	LTMP	60	30 %	8 %
2	"	30	34 %	8 %
3	"	10	63 %	6 %
4	"	5	55 %	9 %
5	LDA	5	37 %	24 %
6	LB1	5	21 %	24 %

The best results were obtained (entries 3 and 4) with LTMP and short reaction times (5-10 min), however small amounts of starting material were recovered. The experimental conditions of entry 3 have been then used to functionalize iodopyrazine **1** (Scheme 3, table 2).

The regioselectivity at the C_3 position has been unambiguously assigned thanks to the coupling constant between H_5 and H_6 ($^3J_{5,6}$= 2.7 Hz).[20] It can be noticed that 2-iodo-3-substituted pyrazines **3-11** resulting from the direct lithiation of **1** were generally obtained with moderate yields, these are slightly lower than those observed during the metallation of chloropyrazine.[21]

Scheme 3



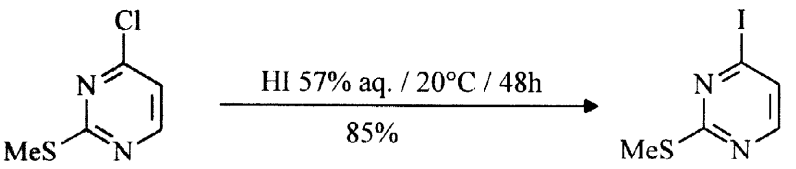
1 **3 - 11**

Table 2.- *Metallation of iodopyrazine 1 and reaction with various electrophiles*

Electrophile	E	Product	Yield	Starting material 1
MeCHO	MeCH(OH)	**3**	55 %	9 %
PhCHO	PhCH(OH)	**4**	66 %	12 %
Ph_2CO	$Ph_2C(OH)$	**5**	78 %	-
PhSSPh	SPh	**6**	82 %	-
$HCONMe_2$	CHO	**7**	26 %	10 %
HCO_2Et	CHO	**7**	19 %	9 %
N-Formylpiperidine	CHO	**7**	30 %	10 %
$ClSiMe_3$	$SiMe_3$	**8**	45 %	-
MeI	Me	**9**	56 %	14 %
CO_2	COOH	**10**	24 %	-
I_2	I	**11**	73 %	-

As we planned to extend study of metallation induced by iodine in pyrimidines, we chose to start from the commercially available 4-chloro-2-methylthiopyrimidine which allowed us to synthesize the corresponding iodo derivative **2** with 85% yield (Scheme 4) according to the procedure described by Undheim[22] (Scheme 4).

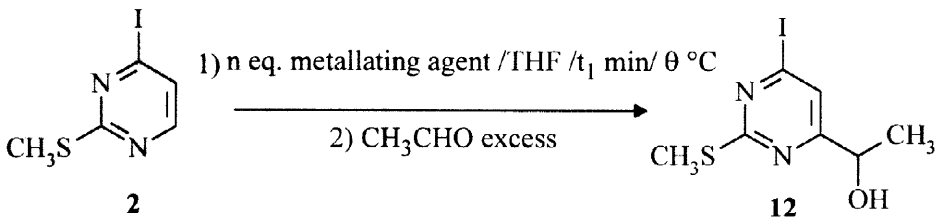
Scheme 4



2

The most efficient conditions of the metallation of 4-iodo-2-methylthiopyrimidine **2** were determined with acetaldehyde as the electrophile. Various metallating agents (LDA, LTMP, LB1) were used in different amounts, and various reaction times and temperatures were tested (Scheme 5, Table 3).

Scheme 5



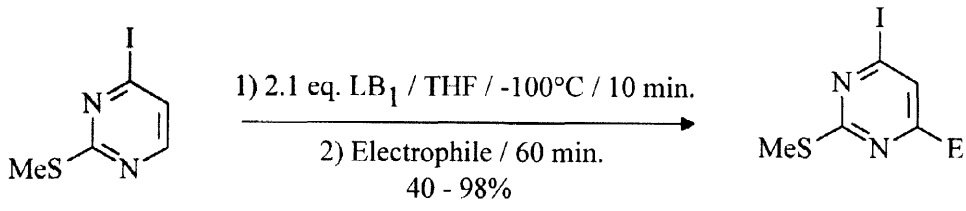
2 **12**

Table 3.- *Metallation of 2 and reaction with acetaldehyde*

Entry	Metallating agent	n equiv.	θ°C	t_1 min.	12	Starting material
1	LDA	1.1	- 70°C	5	-	59%
2	«	«	«	10	-	41%
3	LTMP	«	- 100°C	5	8%	64%
4	«	«	- 100°C	10	20%	60%
5	«	2.1	- 100°C	5	33%	54%
6	«	«	- 70°C	5	22%	-
7	«	«	- 100°C	10	63%	-
8	LB1	«	- 70°C	10	13%	-
9	LB1	«	- 100°C	10	96%	-

Metallation was observed only when LTMP or LB1 were used as metallating agents, and the compound **12** exhibited a total regioselectivity at the C_6 position, ortho to the ring nitrogen. The alcohol **12** was obtained in lower yields at – 70°C (entries 6,8) or when 1.1 equivalent of alkylamide was used (entries 3,4), the yield became better with 2.1 equivalents of metallating agent and a lower temperature (entries 5,7,9). The best result was obtained with the strongest base LB1 (2.2 eq.) at –100°C with 10 minutes for reaction time (entry 9), affording **12** in good yield. These experimental conditions have been used to functionalize 4-iodo-2-methylthiopyrimidine **2** (Scheme 6, Table 4).

Scheme 6



2 **12 - 18**

Table 4.- *Metallation of 2 and reaction with various electrophiles.*

Electrophile	E	Compound	yield
CH_3CHO	$CH_3CH(OH)$	**12**	96%
PhCHO	PhCH(OH)	**13**	63%
Ph_2CO	$Ph_2C(OH)$	**14**	72%
MeI	Me	**15a**	50%
	Et	**15b**[24]	24%
$ClSiMe_3$	$SiMe_3$	**16**	75%
HCO_2Et	CHO	**17**	40%
I_2	I	**18**	57%
«	I	**18**	98%*

**Reaction was performed with 120 minutes for reaction time of iodine with lithio derivative*

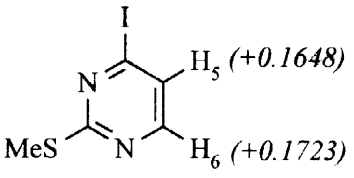
It can be noticed that 4-iodo-2-methylthio-6-substituted pyrimidines **12-18** were obtained with moderate to good yields. When iodine was used as the electrophile, the yield was improved when the reaction time was increased to 120 minutes.

DISCUSSION

The various iodo-substituted pyrazines or pyrimidines resulting from functionalization via the metallation of **1**or **2** have been obtained with moderate to good yields. This provides us an unexpected result which contrasts with attempts to metallate 3-iodopyridine.[11] In comparaison with results obtained during metallation of diazines without ortho-directing group,[17] these results indicate that the iodine atom, though being a weak ortho-directing group, makes the reaction of metallation easier and favours better the yields of iodosubstituted pyrazines and pyrimidines.

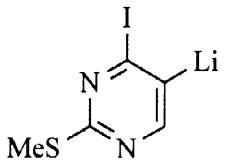
With 2-iodopyrazine **1,** lithiation occurred at the C_3 position, the focus of the simultaneous directing effects of iodine and ring nitrogen. On the other hand, with 4-iodo-2-methylthiopyrimidine **2**, iodine and ring nitrogen compete to induce the metallation. The regioselectivity at the C_6 position observed with **2** can be discussed in terms of kinetic or thermodynamic control of the reaction using semiempirical calculations. In case of kinetic control, the examination of net charges of H_5 and H_6 could be considered in first approximation, although such calculations do not take into account possible complexations and steric effects. After the optimization of geometry of **2** using the MMX method, the net charges of H_5 and H_6, determined by the AM1[25] method, are different, H_6 being slightly more electropositive than H_5. This is in favour of a kinetic deprotonation at C_6 (Scheme 7).

Scheme 7

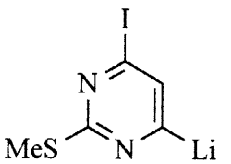


2

Net charges by AM1



$\Delta H_f = 86.2$ Kcal/mol



$\Delta H_f = 75.2$ Kcal/mol

Heats of formation by PM3

If deprotonation is thermodynamically controlled, then it could be assumed that the heats of formation, determined by semiempirical method, could be examined in a simple approach to account for the regioselectivity. Li/PM3 method which appears to be one of the most efficient methods for calculations of systems containing lithium[26] has been used. The PM3 results are generally in acceptable agreement with the energetic ordering and structural data obtained from *ab initio* calculations.[27] The examination of heats of formation of lithio derivatives indicates that the C_6 lithio derivative is more stable than those at C_5 (Scheme 7).

The steric hindrance factor could also be taken into account. Results dealing with conditions of the metallation of **2** (Scheme 5, Table 3) indicated that only LTMP or LB1, stronger and bulkier bases than LDA,[23] allowed deprotonation. So it could be assumed in this case that the steric hindrance of the metalling agent was also in favour of the regioselectivity at C_6.

Thus consideration of steric hindrance of the bases and determination of the site of metallation (kinetic or thermodynamic) by semiempirical calculations are in agreement with the unexpected regioselectivity at C_6.

CONCLUSION

For the first time, directed lithiation of iododiazines has been sucessfully achieved using strong bases such as LTMP or LB1. Further reaction of the lithio derivatives with various electrophiles allowed access to functionalized pyrazine or pyrimidines with good yields. These results could be mainly assigned to the simultaneous effect of electron deficiency of the nucleus of diazines and the iodine atom.

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage. The ^1H, ^{19}F and ^{13}C NMR spectra were recorded in deuteriochloroform on a Bruker AC 200 instrument. Microanalyses were performed on a Carlo Erba CHNOS 1160 apparatus. Mass spectra were recorded at 70 eV (EI) on a JEOL JMS-AX 500 spectrometer.

Tetrahydrofuran 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). Metallations were performed under an argon atmosphere. Reagents were handled with syringes through septa.

General procedure for metallation

A solution of *n*-butyllithium 1.6 or 2.5 M in hexane (n eq.) was added to cooled (-50°C), stirred, anhydrous tetrahydrofuran (20 ml) under an atmosphere of dry argon. Then 2,2,6,6-tetramethylpiperidine (TMPH) or N,N-*tert*-butyl(1-isopropyl)pentylamide (n eq.) was added. The mixture was warmed to 0°C for 20 minutes. The mixture was then carried to θ_1. The pyrazine dissolved in 5 ml of tetrahydrofuran was added and the mixture was stirred for a time t_1 at θ_1. A solution of electrophile in 5 ml of tetrahydrofuran 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 (2ml), ethanol (2ml) and tetrahydrofuran (5ml). The solution was warmed to room temperature, and made slightly basic with saturated sodium hydrogen carbonate solution. When the electrophile was iodine, the solution was decolorised with sodium thiosulphate and evaporated nearly to dryness. The residue was extracted with dichloromethane (3x20ml). The organic extract was dried over magnesium sulfate and evaporated. The crude product was purified by column chromatography on silica gel, distillation or sublimation.

2-iodopyrazine (1): Chloropyrazine (7.5 ml, 84 mmol) was added to a mixture of acetonitrile (100ml), acetic acid (9.6ml), sulfuric acid (0.5 ml) and sodium iodide (30g, 0.2 mol). The mixture was refluxed for 5 hours. After cooling the solvent was removed under reduced pressure. After addition of water (100ml), the solution was basified to pH 8 with sodium hydrogen carbonate, extracted with dichloromethane (3x100ml). The organic extract was washed with saturated solution of sodium thiosulfate, then dried over magnesium sulfate. Solvent removal afforded a crude product which was purified by distillation to give 16.9 g (80%) of **1** as a colorless liquid, bp 65°C/0.4 mm Hg; ^{1}H NMR ($CDCl_3$): δ 8.76 (d, 1H, $J_{3,6}$ = 1.5 Hz, H_3); 8.41 (d, 1H, $J_{6,5}$ = 2.4 Hz, H_5 or H_6); 8.29 (dd, 1H, H_5 or H_6); ^{13}C NMR ($CDCl_3$) 153.0 (C_3); 145.7 (C_6); 142.8 (C_5); 118.5 (C_2). Anal Calcd for $C_4H_3IN_2$ (205.99): C, 23.32; H, 1.46; N, 13.59. Found: C, 23.6; H, 1.4; N, 13.8.

4-iodo-2-methylthiopyrimidine (2) : Synthesis of **2** was achieved according to the procedure described by Undheim.[16b] Yield 85%, m.p. 52-53°C (Lit 52-53°C), ^{1}H NMR ($CDCl_3$): δ 8.09 (d, 1H, $J_{5,6}$=4.5 Hz, H_6) ; 7.45 (d, 1H, H_5) ; 2.53 (s, 3H, Me); ^{13}C NMR ($CDCl_3$) : δ 173 (C_2); 156 (C_6) ; 129 (C_4) ; 127 (C_5) ; 14 (MeS). Anal Calcd for $C_5H_5IN_2$ S (252.08): C, 23.82; H, 1.99; N, 11.11. Found: C, 23.8; H, 1.9; N, 11.0.

3-(1-hydroxyethyl)-2-iodopyrazine (3) : Metallation of **1** (200 mg, 0.97 mmol) according to the general procedure with *n*- BuLi 2.5M (0.43 ml, 1.1 eq.), TMPH (0.2 ml, 1.2 eq.), t_1 = 5 min, θ_1= - 78°C, followed by reaction with acetaldehyde (2ml, 37 eq.), t_2 = 60 min, θ_2 = - 78°C afforded after purification by column chromatography (silica, eluent : petroleum ether/ethylacetate (2/1)) 133 mg (55%) of **3** as a yellow oil; ^{1}H NMR ($CDCl_3$): δ 8.39 (d, 1H, $J_{5,6}$ = 2.4 Hz, H_5 or H_6); 8.21 (d, 1H, $J_{6,5}$ = 2.4Hz, H_5 or H_6); 5.02 (m, 1H, CH); 3.80 (d, 1H, J = 8.3 Hz, OH); 1.43 (d, 3H, J = 6.4 Hz, CH_3) Anal Calcd for $C_6H_7IN_2O$ (250.04): C, 28.82; H, 2.82; N, 11.20. Found: C, 28.9; H, 2.7; N, 11.1.

2-iodo-3-(phenylhydroxymethyl)pyrazine (4): metallation of **1** (200 mg, 0.97 mmol) according to the general procedure with *n*- BuLi 2.5M (0.43 ml, 1.1 eq.), TMPH (0.2 ml, 1.2 eq.), t_1 = 5 min, θ_1= - 78°C, followed by reaction with benzaldehyde (108 mg, 1.1mmol), t_2 = 60 min, θ_2= - 78°C, afforded after purification by column chromatography (silica, eluent : petroleum ether/ethyl acetate (2/1)) 200 mg (66%) of **4** as a yellow oil; ^{1}H NMR ($CDCl_3$): δ 8.46 (d, 1H, J = 2.4 Hz); 8.24 (d, 1H); 7.27 (m, 5H, Phenyl); 5.94 (d, 1H, J = 7.8 Hz, CH); 4.72 (d, 1H, OH). Anal Calcd for $C_{11}H_9IN_2O$ (312.11): C, 42.33; H, 2.90; N, 8.97. Found: C, 42.5; H, 2.7; N, 9.0.

2-iodo-3-(diphenylhydroxymethyl)pyrazine (5) : Metallation of **1** (200 mg, 0.97 mmol) according to the general procedure with *n*- BuLi 2.5M (0.43 ml, 1.1 eq.), TMPH (0.2 ml, 1.2 eq.), t_1 = 5 min, θ_1= - 78°C, followed by reaction with benzophenone (194 mg, 1.1mmol), t_2 = 60 min, θ_2= - 78°C, afforded after purification by column chromatography (silica, eluent : petroleum ether/ethyl acetate (4/1)) 300 mg (80%) of **5** as a white solid, mp 142-143°C; ^{1}H NMR ($CDCl_3$): δ 8.46 (d, 1H, J = 2.2Hz); 8.28 (d, 1H); 7.31 (m, 10H

Phenyl); 5.59 (s,1H, OH). Anal Calcd for $C_{17}H_{13}IN_2O$ (388.21): C, 52.99; H, 3.37; N, 7.21. Found: C, 52.7; H, 3.5; N, 7.2.

2-iodo-3-phenylthiopyrazine (6) : Metallation of **1** (200 mg, 0.97 mmol) according to the general procedure with *n*- BuLi 2.5M (0.43 ml, 1.1 eq.), TMPH (0.2 ml, 1.2 eq.), t_1 = 5 min, θ_1= - 78°C, followed by reaction with diphenyl sulfide (233 mg, 1.1mmol), t_2 = 60 min, θ_2= - 78°C, afforded after purification by column chromatography (silica, eluent : petroleum ether/ethyl acetate (4/1)) 250 mg (82%) of **6** as a white solid, mp 91-92°C; ^{1}H NMR ($CDCl_3$): δ 8.11 (d, 1H, J = 2.5Hz); 7.94 (d, 1H); 7.46 (m, 5H Phenyl). Anal Calcd for $C_{10}H_7IN_2S$ (314.15): C, 38.23; H, 2.24; N, 8.91. Found: C, 38.3; H, 2.3; N, 8.8.

2-iodo-3-formylpyrazine (7) : Metallation of **1** (200 mg, 0.97 mmol) according to the general procedure A with *n*- BuLi 2.5M (0.43 ml, 1.1 eq.), TMPH (0.2 ml, 1.2 eq.), t_1 = 5 min, θ_1= - 78°C, followed by reaction with N-formylpiperidine (0.2 ml, 2mmol), t_2 = 60 min, θ_2= - 78°C, afforded after purification by column chromatography (silica, eluent : petroleum ether/ethyl acetate (2/1)) 250 mg (30%) of **7** as a yellow liquid; ^{1}H NMR ($CDCl_3$): δ 10.11 (s, 1H,CHO); 8.69 (d, 1H, J = 2.3Hz); 8.49 (d, 1H). Anal Calcd for $C_5H_3IN_2O$ (233.99): C, 25.66; H, 1.29; N, 11.97. Found: C, 25.9; H, 1.4; N, 12.1.

2-iodo-3-trimethylsilylpyrazine (8) : Metallation of **1** (200 mg, 0.97 mmol) according to the general procedure with *n*- BuLi 2.5M (0.43 ml, 1.1 eq.), TMPH (0.2 ml, 1.2 eq.), t_1 = 5 min, θ_1= - 78°C, followed by reaction with trimethylsilyl chloride (0.3 ml, 2.5 mmol), t_2 = 60 min, θ_2= - 78°C, afforded after purification by column chromatography (silica, eluent : petroleum ether/ethylacetate (4/1)) 121 mg (45%) of **8** as a yellow liquid; ^{1}H NMR ($CDCl_3$): δ 8.56 (d, 1H, J = 2.4Hz); 8.13 (d, 1H); 0.43 (s, 9H, $SiMe_3$). Anal Calcd for $C_7H_{11}IN_2Si$ (278.17): C, 30.22; H, 3.98; N, 10.07. Found: C, 30.1; H, 3.9; N, 9.8.

2-iodo-3-methylpyrazine (9) : Metallation of **1** (200 mg, 0.97 mmol) according to the general procedure with *n*- BuLi 2.5M (0.43 ml, 1.1 eq.), TMPH (0.2 ml, 1.2 eq.), t_1 = 5 min, θ_1= - 78°C, followed by reaction with iodomethane (0.6 ml, 9.7 mmol), t_2 = 60 min, θ_2= - 78°C, afforded after purification by column chromatography (silica, eluent : ether/cyclohexane (1/3)) and sublimation 120 mg (56%) of **9** as a white solid, mp 24-25°C; ^{1}H NMR ($CDCl_3$): δ 8.29 (d, 1H, J = 2.3Hz); 8.07 (d, 1H); 2.64 (s, 3H, Me). Anal Calcd for $C_5H_5IN_2$ (220.01): C, 27.30; H, 2.29; N, 12.73. Found: C, 27.3; H, 1.9; N, 12.5.

(3-iodo-2-pyrazine)carboxylic acid (10) : Metallation of **1** (200 mg, 0.97 mmol) was performed according to the general procedure with *n*- BuLi 2.5M (0.43 ml, 1.1 eq.), TMPH (0.2 ml, 1.2 eq.), t_1 = 5 min, θ_1= - 78°C, followed by reaction with carbonic anhydride in excess. Hydrolysis was performed at 0°C with 50 ml water, then acidified to pH 2 with aqueous hydrogen chloride. After extraction with ether (4x30ml), the organic extract was dried over magnesium sulfate and evaporated to give 60mg (24%) of **10** as a white solid,
mp > 250°C; ^{1}H NMR ($CDCl_3$): δ 8.41 (d, 1H, J = 2.5Hz); 8.25 (d, 1H). Anal Calcd for $C_5H_3IN_2O_2$ (250.00): C, 24.02; H, 1.21; N, 11.20. Found: C, 23.8; H, 1.1; N, 11.0.

2,3-diiodopyrazine (11) : Metallation of **1** (200 mg, 0.97 mmol) according to the general procedure with *n*-BuLi 2.5M (0.43 ml, 1.1 eq.), TMPH (0.2 ml, 1.2 eq.), t_1 = 5 min, θ_1= - 78°C, followed by reaction with iodine (500 mg, 2 mmol), t_2 = 60 min, θ_2= - 78°C afforded after purification by column chromatography (silica, eluent : petroleum ether/ethyl acetate (4/1)) 235 mg (73%) of **11** as a white solid, mp 97-98°C; ^{1}H NMR ($CDCl_3$): δ 8.25 (s, H_5, H_6). Anal Calcd for $C_4H_2I_2N_2$ (331.88): C, 14.47; H, 0.60; N, 8.44. Found: C, 14.5; H, 0.4; N, 8.4.

4-iodo-2-methylthio-6-(1-hydroxyethyl)-pyrimidine (12) : Metallation of **2** (200 mg, 0.79 mmol) according to the general procedure with *n*-BuLi 2.5M (0.66 ml, 2.1 eq.), N,N-*tert*-butyl(1-isopropyl)pentylamine (0.316 g, 2.15 eq.), t_1 = 10 min, θ_1= - 100°C, followed by reaction with acetaldehyde (1 ml, 18 eq.), t_2 = 60 min, θ_2 = - 100°C afforded after purification by column chromatography (silica, eluent : dichloromethane/ethyl acetate (1/1)) gave 225 mg (96%) of **12** as a colorless oil; ^{1}H NMR ($CDCl_3$): δ 7.46 (s, 1H, H_5) ; 4.66 (m, 1H, CH);

3.65 (d, 1H, J = 4.9 Hz, OH); 2.47 (s, 3H, Me) ; 1.41 (d, 3H, J = 6.7 Hz, CH_3). Anal Calcd for $C_7H_9IN_2OS$ (296.13): C, 28.39; H, 3.09; N, 9.46. Found: C, 28.5; H, 3.1; N, 9.5.

4-iodo-2-methylthio-6-(1-phenylhydroxymethyl)pyrimidine (13) : Metallation of **2** (200 mg, 0.79 mmol) according to the general procedure with *n*-BuLi 2.5M (0.66 ml, 2.1 eq.), N,N-*tert*-butyl(1-isopropyl)pentylamine (0.316 g , 2.15 eq.), t_1 = 10 min, θ_1= - 100°C, followed by reaction with benzaldehyde (90 µl, 0.87 mmol), t_2 = 60 min, θ_2= - 100°C, afforded after purification by column chromatography (silica, eluent : dichloromethane) gave 178 mg (63%) of **13** as a colorless oil; ^{1}H NMR ($CDCl_3$): δ 7.35-7.23 (m, 6H, H_5, Phenyl); 5.51 (d, 1H, CH); 4.31 (d, 1H, J = 4.0 Hz, OH) ; 2.50 (s, 3H, SMe). Anal Calcd for $C_{12}H_{11}IN_2OS$ (358.2): C, 40.42; H, 3.06; N, 7.81. Found: C,40.4; H, 2.9; N, 7.8.

4-iodo-2-methylthio-6-(diphenylhydroxymethyl)pyrimidine (14) : Metallation of **2** (200 mg, 0.79 mmol) according to the general procedure with *n*- BuLi 2.5M (0.66 ml, 2.1 eq.), N,N-*tert*-butyl(1-isopropyl)pentylamine (0.316 g, 2.15 eq.), t_1 = 10 min, θ_1= - 100°C, followed by reaction with benzophenone (164 mg, 0.87 mmol), t_2 = 60 min, θ_2= - 100°C, afforded after purification by column chromatography (silica, eluent : cyclohexane/ethyl acetate (15/1)) 347 mg (72%) of **14** as a yellow solid, mp 37-38°C; ^{1}H NMR ($CDCl_3$): δ 7.32-7.24 (m, 11H, H_5, Phenyl); 5.02 (s, 1H, OH) ; 2.58 (s, 3H, SMe). Anal Calcd for $C_{18}H_{15}IN_2OS$ (434.30): C, 49.78; H, 3.38; N, 6.10. Found: C, 49.9; H, 3.5; N, 6.3.

4-iodo-2-methylthio-6-methylpyrimidine (15a) : Metallation of **2** (200 mg, 0.79 mmol) according to the general procedure with *n*- BuLi 2.5M (0.66 ml, 2.1 eq.), N,N-*tert*-butyl(1-isopropyl)pentylamine (0.316 g , 2.15 eq.), t_1 = 10 min, θ_1= - 100°C, followed by reaction with iodomethane, (250 µl, 4 mmol) t_2 = 60 min, θ_2= - 100°C, afforded after purification by column chromatography (silica, eluent : dichloromethane/ethyl acetate (3/2)) 105 mg (82%) of **15a** as a white solid, mp 100-101°C; ^{1}H NMR ($CDCl_3$): δ 7.26 (s, 1H, H_5); 2.50 (s, 3H, SMe) ; 2.32 (s, 3H, Me). Anal Calcd for $C_6H_7IN_2S$ (266.11): C, 27.08; H, 2.65; N, 10.53. Found: C, 27.4; H, 2.6; N, 10.5.

4-iodo-2-methylthio-6-ethylpyrimidine (15b) : Metallation of **2** (200 mg, 0.79 mmol) according to the previous procedure afforded after purification by column chromatography (silica, eluent : dichloromethane/ethyl acetate (3/2)) 53 mg (24%) of **15b** as a white solid, mp 67-68°C; ^{1}H NMR ($CDCl_3$): δ 7.24 (s, 1H, H_5); 2.56 (s, 2H, J = 6.5Hz, CH_2) ; 2.50 (s, 3H, SMe) ; 2.32 (s, 3H, Me). Anal Calcd for $C_7H_9IN_2S$ (280.11): C, 29.98; H, 3.21; N, 9.99. Found: C, 29.9; H, 3.2; N, 10.1.

4-iodo-2-methylthio-6-trimethylsilylpyrimidine (16) : Metallation of **2** (200 mg, 0.79 mmol) according to the general procedure with *n*- BuLi 2.5M (0.66 ml, 2.1 eq.), N,N-*tert*-butyl(1-isopropyl)pentylamine (0.316 g, 2.15 eq.), t_1 = 10 min, θ_1= - 100°C, followed by reaction with trimethylsilyl chloride (0.3 ml, 2.5 mmol), t_2 = 60 min, θ_2= - 100°C, afforded after purification by column chromatography (silica, eluent : dichloromethane /cyclohexane (1/1)) 192 mg (75%) of **16** as a white solid, mp 78-79°C; ^{1}H NMR ($CDCl_3$): δ 7.47 (s, 1H, H_5); 2.50 (s, 3H, SMe) ; 0.26 (s, 9H, $SiMe_3$). Anal Calcd for $C_8H_{13}IN_2SSi$ (324.26): C, 29.63; H, 4.04; N, 8.64. Found: C, 29.8; H, 4.1; N, 8.8.

4-iodo-2-methylthio-6-formylpyrimidine (17) : Metallation of **2** (200 mg, 0.79 mmol) according to the general procedure with *n*- BuLi 2.5M (0.66 ml, 2.1 eq.), N,N-*tert*-butyl(1-isopropyl)pentylamine (0.316 g, 2.15 eq.), t_1 = 10 min, θ_1= - 100°C, followed by reaction with ethyl formiate (260 µl, 3.2 mmol), t_2 = 60 min, θ_2= - 100°C, afforded after purification by column chromatography (silica, eluent : dichloromethane /cyclohexane (3/2)) 89 mg (40%) of **17** as a white solid, mp 145-146°C; ^{1}H NMR ($CDCl_3$): δ 9.66 (s, 1H,CHO); 7.81 (s, 1H, H_5); 2.56 (s, 3H, SMe). Anal Calcd for $C_6H_5IN_2OS$ (280.09): C, 25.73; H, 1.80; N, 10.00. Found: C, 26.0; H, 1.7; N, 10.0.

2-methylthio-4,6-diiodopyrimidine (18) : Metallation of **2** (200 mg, 0.97 mmol) according to the general procedure with *n*- BuLi 2.5M (0.66 ml, 2.1 eq.), N,N-*tert*-butyl(1-isopropyl)pentylamine (0.316 g, 2.15 eq.), t_1 = 10 min, θ_1= - 100°C, followed by reaction with iodine (600 mg, 2.3 mmol), t_2 = 120 min, θ_2= - 100°C afforded after purification by column chromatography (silica, eluent : dichloromethane /cyclohexane (1/1)) 292 mg (98%) of **18** as a white solid, mp 152-153°C; ^{1}H NMR ($CDCl_3$): δ 7.81 (s, 1H, H_5); 2.56 (s, 3H, SMe). Anal Calcd for $C_5H_4I_2N_2S$ (377.97): C, 15.88; H, 1.06; N, 7.41. Found: C, 15.9; H, 1.0; N, 7.3.

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