Metalation of Bromodiazines. Diazines XL

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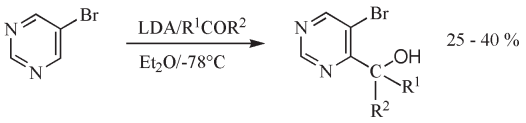
Received July 27, 2004

The syntheses of 2-bromopyrazine, 2,4-dibromopyrimidines, and 3-bromo-6-phenylpyrazine were improved and their metalation with lithium alkylamides was studied.

J. Heterocyclic Chem., **42**, 509 (2005).

The *ortho* directed metalation of various halogenated diazines has been extensively studied [1], however only one example of metalation of a bromo diazine: the 5-bromopyrimidine, has been reported in the literature by Kress [2] (Scheme 1).

Scheme 1



In the pyridine series, the metalation reaction of -2, -3 and -4-bromopyridines has been investigated [3,4] and was generally successful with 1 equivalent of lithium di*iso*-propylamide at –78 °C in tetrahydrofuran.

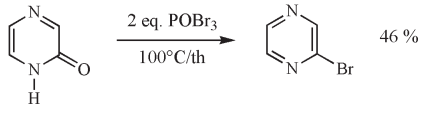
Our purpose was to study the metalation reaction of bromo derivatives of diazines. An example for each diazine series was chosen: 2-bromopyrazine, 2,6-dibromopyrimidine and 3-bromo-6-phenylpyridazine. This choice was mainly governed by the accessibility to these bromo derivatives.

Synthesis of 2-Bromopyrazine **1**.

After completion of this work, a synthesis of **1** was published by Schlosser [5] using chloropyrazine and bromotrimethylsilane, with a 49 % yield. We tested several methods: direct metalation of pyrazine [6], Craig's method [7] starting from aminopyrazine, bromine-chlorine exchange with potassium bromide [8], or phosphorous tribromide [9].

All these methods had some drawbacks (poor yields or difficulty to purify) and all the things considered, we chose the old method of Spoerri [10] (Scheme 2) starting from pyrazinone which was synthesized by the method of Konokahara [11] using glycinamide chlorhydrate and glyoxal with a 70 % yield.

Scheme 2



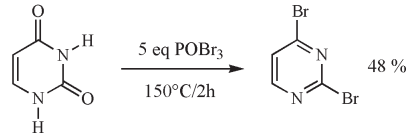
pyrazinone **1**

The synthesis of Spoerri used a mixture of phosphorous oxybromide and pentabromide as brominating agent and gave a mixture of monobromo and dibromopyrazine. We did not use pentabromide to avoid the formation of the dibromo derivative. With 2 equivalents of phosphorous oxybromide, no dibromopyrazine was formed and we obtained a 46 % yield of **1** after distillation.

Synthesis of 2,4-Dibromopyrimidine **2**.

The same route as above was used starting from uracil. This reaction was described by Gronowitz [12] with a 10 % yield. We were able to improve this yield to 48 % by changing the purification process (column chromatography instead of distillation (Scheme 3).

Scheme 3

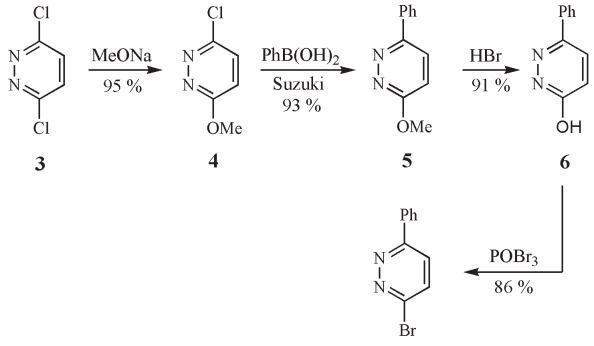


uracil **2**

Synthesis of 3-Bromo-6-phenylpyridazine **7**.

Starting from 2,6-dichloropyridazine **3**, the following route was developed (Scheme 4).

Scheme 4



3 **4** **5** **6** **7**

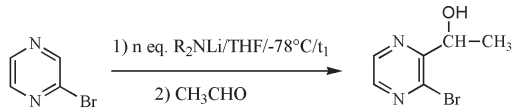
After substitution of a chlorine atom by a methoxy group a Suzuki cross coupling was performed and followed by hydrolysis of the methoxy group with hydrobromic acid. The reaction of **6** with phosphorous oxybromide afforded **7** with a 69 % overall yield from **3**.

Metalation of the Bromodiazines **1**, **2**, **7**.

Metalation of 2-Bromopyrazine **1**.

Using acetaldehyde as electrophile, various experimental parameters were tested: nature of the metalating agent, lithium di*iso*propylamide (LDA) or 2,2,6,6-lithium tetramethylpiperidide (LTMP), number of equivalents, reaction time. (Table 1, Scheme 5)

Scheme 5



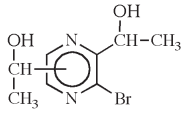
1 **8**

Table 1

Optimization of the Metalation Conditions for **1**

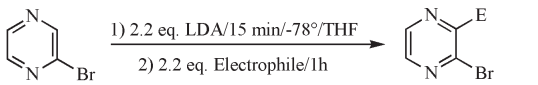
Entry	*n* eq	R_2NLi	t_1 min	yield % of 8
1	1.2	LTMP	15	12
2	1.2	LTMP	30	5
3	2.2	LTMP	15	38*
4	1.2	LDA	15	14
5	2.2	LDA	15	77
6	3.2	LDA	15	62

* beside 32 % of trisubstituted compound:



The use of 1.2 equivalents of metalating agent gave poor yields (entries 1,2,4); an excess (2.2 equiv.) of 2,2,6,6-lithium tetramethylpiperidide led to some dimetalation (entry 3). The use of 2.2 equivalents of lithium di*iso*propylamide afforded **8** with a good yield (entry 5), a further excess of lithium di*iso*propylamide decreased the yield (entry 6).

Scheme 6



9 E = -CH(OH)Ph
10 -SPh
11 -I

Using the experimental conditions of entry 5, other electrophiles were reacted (Table 2, Scheme 6).

Table 2

Metalation of **1** and Reaction with Electrophiles

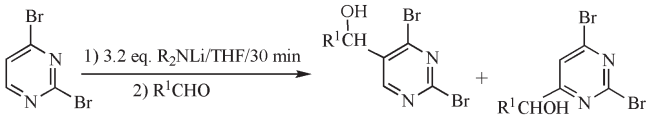
Entry	electrophile	product	Yield
1	PhCHO	9	69 %
2	Ph_2S_2	10	53 %
3	I_2	11	50 %
4	Me_3SiCl	–	0 %
5	Bu_3SnCl	–	0 %

When Me_3SiCl or Bu_3SnCl were used as electrophiles (entry 4,5) no isolable products were found and no starting material was recovered.

Metalation of 2,4-Dibromopyrimidine **2**.

The experimental conditions used for **1** were tested but neither isolable products nor starting material were observed. So, other experimental conditions were tested (Scheme 7, Table 3).

Scheme 7



2 **12a** **13a** **12b** **13b**

R^1 = Me
R^1 = *p*OMePh

Table 3

Metalation of **2**

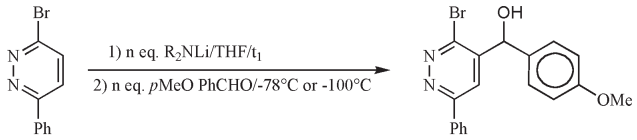
Entry	R_2NLi	R^1	temp	Products	Yields a	Yields b
1	LDA	Me	-78°C	12	5 %	–
2	LDA	Me	-100°C	12	20 %	5 %
3	LTMP	Me	-100°C	12	–	21 %
4	LDA	*p*OMePh	-100°C	13	26 %	2 %
5	LTMP	*p*OMePh	-100°C	13	8 %	24 %

The use of lithium di*iso*propylamide led to a mixture of monometalation products. The main product was substituted *ortho* to the bromine atom (entries 1,2,4). By contrast the use of 2,2,6,6-lithium tetramethylpiperidide led to a main product substituted in the position α to the ring nitrogen (entries 3,5) and some 5,6 disubstituted product ($\simeq$ 20 %) was found in the ^1H NMR spectrum of the raw material and could not be isolated.

Metalation of 3-Bromo-6-phenylpyridazine **7**.

As for **1**, metalation was first tested using acetaldehyde as electrophile, but the alcohol so obtained was not stable and decomposed during workup, the use of anisaldehyde instead of acetaldehyde solved the problem (Scheme 8, Table 4).

Scheme 8



7 **14**

Table 4

Metalation of **7**

Entry	*n* eq	R_2NLi	t_1 min	temp	yield of 14
1	1.2	LTMP	30	-78°C	25 %
2	2.2	LTMP	30	-78°C	37 %
3	2.2	LDA	30	-78°C	43 %
4	2.2	LDA	15	-78°C	55 %
5	2.2	LDA	30	-100°C	84 %

In this case also, a twofold excess of metalating agent was necessary, (entries 1, 2). A cooling of the reaction medium to –100 °C with lithium di*iso*propylamide as metalating agent (entry 5) allowed us to obtain a good yield of compound **14**.

Conclusion.

Our results indicate that it is possible to metalate bromodiazines, however, the reaction is critical and the experimental conditions must be carefully studied. Contrary to the results with chloro, iododiazines or bromopyridines, a twofold or more excess of lithium di*iso*propylamide was necessary to achieve the metalation.

EXPERIMENTAL

General Data.

Melting points were determined on Kofler apparatus and are uncorrected. The ^{1}H NMR spectra were recorded at 300 MHz on a Bruker Avance-300 NMR spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) downfield from an internal standard, tetramethylsilane in deuteriochloroform, or hexamethyldisiloxane in d_6-dimethylsulfoxide. Coupling constants (*J*) are given in hertz (Hz). Elemental analyses were performed on a Carlo-Erba CHN apparatus. Mass spectra were recorded on a JEOL JMS-AX500 mass spectrometer; samples were vaporized in a direct inlet system. Column chromatography was carried out on SiO_2, Merck – Geduran SI60 (70-230 mesh). 3-Methoxy-6-phenylpyridazine (**5**) and 6-Phenyl-3-(*2H*)-pyridazinone (**6**) were prepared following reference [14].

2-Bromopyrazine (**1**).

A mixture of (*2H*)-pyrazinone (4.2 g, 0.044 mmol) and phosphorous oxybromide (25 g, 0.088 mole) was heated at 105 °C for 1.5 h. After cooling to room temperature, the mixture was poured on crushed ice (300 g) and made neutral with sodium hydrogenocarbonate. The mixture was extracted with dichloromethane (2 x 100 mL). The extract was dried with magnesium sulfate and evaporated under vacuum. The residue was distilled under vacuum (70 °C, 12 torr). 2-Bromopyrazine (3.2 g, 46 %) was obtained as a colorless liquid. Spectral characteristics identical to literature [8].

2,4-Dibromopyrimidine (**2**).

A mixture of uracil (2.7 g, 0.024 mmol) and phosphorous oxybromide (38 g, 0.12 mol) was heated at 150 °C for 2 h. After cooling at room temperature, the mixture was poured on crushed ice (500 g) and made neutral with sodium hydrogen carbonate. The mixture was extracted with dibromomethane (2 x 150 mL). The extract was dried with magnesium sulfate and evaporated under vacuum. The crude product (5 g) was purified by silica gel chromatography the eluent was a mixture of cyclohexane and ethyl acetate (elution gradient 80/20 to 50/50). 2,4-Dibromopyrimidine (2.7 g, 48 %) was obtained as a white solid mp 66-68 °C. Spectral characteristics identical to literature [12]. In this publication [12], 2,4-dibromopyrimidine was obtained with a 10 % yield by distillation.

3-Bromo-6-phenylpyridazine (**7**).

A mixture of 6-phenyl-3-(*2H*)-pyridazinone **6** (1.2 g, 7 mmol) and phosphorous oxybromide (7 g, 24 mmol) was heated at 80 °C for 1.5 h. After cooling the mixture was poured on ice (100 g), then neutralized at 0 °C with sodium hydrogenocarbonate. The aqueous phase was extracted with dichloromethane (2 x 30 mL). After drying with magnesium sulfate and evaporation of the solvent, 3-bromo-6-phenylpyridazine (1.4 g, 86 %) was obtained as a white solid mp 169 °C. ^{1}H NMR: δ (ppm) = 8.04 (m, 2H, H_{Ph}); 7.71 (dd, 2H, $H_4 + H_5$); 7.53 (m, 3H, H_{Ph}).

General Procedure for Metalation.

Preparation of the Lithium Alkylamide (LDA, LTMP).

In a three necked flask with magnetic stirring, a thermometer and closed by septa, under an atmosphere of nitrogen, 5 mL of anhydrous tetrahydrofuran were introduced. Di*iso*propylamine or 2,2,6,6-tetramethylpiperidine was added and the mixture cooled to –30 °C. Butyllithium (1.6 or 2.5 *M* in hexanes) was added. The mixture was warmed to 0 °C and kept 20 min at this temperature.

Metalation Procedure.

To the previous solution cooled to T degrees, the substrate to metalate dissolved in V_1 mL of anhydrous THF was added. The metalation was performed at the temperature T during time t_1. Then the electrophile was added and reacted during time t_2.

The hydrolysis of the reaction mixture was performed with a mixture of THF, ethanol and concentrated HCl (2/2/1) at the temperature T. The reaction mixture was warmed to 0 °C and made neutral with a saturated solution of sodium hydrogenocarbonate. It was extracted with dichloromethane (3 x 20 mL). After drying and evaporation the crude product was purified by silica gel chromatography.

The regiochemistry was assigned by HMQC and HMBC experiments.

2-Bromo-3-(1-hydroxyethyl)pyrazine (**8**).

Metalation of 2-bromopyrazine **1** (0.2 g, 1.26 mmol) following the general procedure. V_1 (THF) = 2 mL; T = -78 °C; LDA: *n*-butyllithium 1.6 *M* (1.7 mL, 2.8 mmol, 2.2 equiv.), di*iso*-propylamine (0.4 mL, 2.9 mmol, 2,3 equiv.), t_1 = 15 min; t_2 = 1 h; electrophile: acetaldehyde (1 mL). Dichloromethane was the eluent used for chromatography. Compound **8** was obtained as a colorless oil (0.2 g, 78 %). ^{1}H NMR ($CDCl_3$): δ (ppm) = 8.50 (d, 1H, $J_{5\text{-}6}$ = 2.3 Hz, H_5); 8.31 (d, 1H, $J_{5,6}$ = 2.3 Hz, H_6); 5.17 (q, 1H, J = 8.3 Hz; J = 6.4 Hz, CH); 3.75 (d, 1H, J_{CHOH} = 8.3 Hz, OH); 1.52 (d, 3H, J = 6.4 Hz, CH_3). ^{13}C NMR: δ (ppm) = 159.1 (C_3); 143.9 (C_6); 142.2 (C_5); 139.8 (C_2); 68 (CH); 23.6 (CH_3). IR (cm^{-1}): 3401, 2977, 2929, 1518, 1442, 1401, 1364, 1320, 1183, 1149, 1110, 1071, 1046, 1017.

Anal. Calcd. for $C_6H_7BrN_2O$ (203,04): C, 35.49; H, 3.48; N, 13.80. Found: C, 35.51; H, 3.52; N, 13.45.

2-Bromo-3-(1-hydroxyphenylmethyl)pyrazine (**9**).

Metalation of 2-bromopyrazine **1** (0.2 g, 1.26 mmol) following the general procedure. V_1(THF) = 2 ml; T = -78 °C; LDA: *n*-butyllithium 1.6 *M* (1.7 mL, 2.8 mmol, 2.2 equiv.), di*iso*propylamine (0.4 mL, 2.9 mmol, 2.3 equiv.). t_1 = 15 min, t_2 = 1 h. Electrophile: benzaldehyde (0.31 ml, 2.8 mmol, 2.2 equiv.). Dichloromethane was the eluent used for chromatography. **9** was obtained as a colorless oil (0.23 g, 69 %). ^{1}H NMR ($CDCl_3$): δ (ppm) = 8.57 (d, 1H, $J_{5\text{-}6}$ = 2,3 Hz); 8.34 (d, 1H, $J_{5\text{-}6}$ = 2.3 Hz, H_6); 7.34 (m, 5H, H_{Ph}); 6.04 (d, 1H, J_{CHOH} = 8.3 Hz, CH); 4.55 (d, 1H, J_{CHOH} = 8.3 Hz, OH). ^{13}C NMR: δ (ppm) = 156.5 (C_3); 143.7 (C_6); 141.5 (C_5); 140.4 (C_2 + C_{Ph}); 128.7 (C_{Ph}); 128.4 (C_{Ph}); 127.7 (C_{Ph}); 73.2 (CH). IR (cm^{-1}): 3400; 3060; 3039; 2925; 1518; 1494; 1454; 1403; 1364; 1186; 1144; 1083; 1037; 864; 758; 699.

Anal. Calcd. for $C_{11}H_9BrN_2O$ (265.11): C, 49.84; H, 3.42; N, 10.57. Found: C, 49.81; H, 3.57; N, 10.32.

2-Bromo-3-phenylsulfanylpyrazine (**10**).

Metalation of 2-bromopyrazine **1** (0.2 g, 1.26 mmol) following the general procedure. V_1(THF) = 2 ml; T = -78 °C; LDA: *n*-butyllithium (1.7 mL, 2.8 mmol, 2.2 equiv.), di*iso*propylamine (0.4 mL, 2.9 mol, 2.2 equiv.). t_1 = 15 min, t_2 = 1h. Electrophile: diphenyl disulfide (0,6 g, 2.8 mmol, 2.3 equiv.).

A mixture dichloromethane/methylcyclohexane (1/1) was used as the eluent for chromatography. Compound **10** was obtained as a white solid (0.18 g, 53 %). mp 108-10 °C. ^{1}H NMR ($CDCl_3$): δ = 8.17 (d, 1H, $J_{5,6}$ = 2,6 Hz, $H_{5\text{ or }6}$); 8.00 (d, 1H, $J_{5,6}$ = 2.6 Hz, H_{5or6}); 7.55 (m, 2H, H_{Ph}); 7.46 (m, 3H, H_{Ph}). ^{13}C NMR: δ (ppm) = 159.2 (C_3); 142.5 (C_5); 139.5 (C_6); 138.2 (C_2); 135.8 (C_{Ph}); 129.8 (C_{Ph}); 129.6 (C_{Ph}), 128.7 (C_{Ph}). IR (cm^{-1}): 3056; 1475; 1440; 1329; 1186; 1024; 859; 747; 688.

Anal. Calcd. for $C_{10}H_7BrN_2S$ (267.15): C, 44.96; H, 2.64; N, 10.49; S, 12.00. Found: C, 45.18; H, 2.68; N, 10.41; S, 11.84.

2-Bromo-3-iodopyrazine (**11**).

Metalation of 2-bromopyrazine **1** (0.2 g, 1.26 mmol) following the general procedure. V_1 (THF) = 2 mL; T = -78 °C; LDA: *n*-butyllithium 1.6 *M* (1.7 mL, 2.8 mmol, 2.3 equiv.), di*iso*propylamine (0.4 mL, 2.9 mmol, 2.2 equiv.). t_1 = 15 min, t_2 = 1 h. Electrophile: iodine (0.7 g, 2.8 mmol, 2.2 equiv.) dissolved in 5 mL of THF. Purification by chromatography with a mixture dichloromethane/methylcyclohexane (40/60). Compound **11** was obtained as a white solid (0.18 g, 50 %), mp 75-77 °C; ^{1}H NMR ($CDCl_3$): δ (ppm) = 8.29 (m, 2H, H_5 and H_6); ^{13}C NMR: δ (ppm) = 149.1 (C_2); 142.6 (C_5,C_6); 123.7 (C_3). IR (cm^{-1}): 1529, 1494, 1421, 1399, 1330, 1163, 1131, 1021, 857, 759.

Anal. Calcd. for $C_4H_2BrIN_2$ (284.9): C, 16.86; H, 0.71; N, 9.83. Found: C, 16.89; H, 0.72; N, 9.62.

2,4-Dibromo-5-(1-hydroxyethyl)pyrimidine (**12a**).

Metalation of 2,4-dibromopyrimidine **2** (0,2 g, 0.84 mmol) following the general procedure. V_1 (THF) = 7 ml; T = -100 °C; LDA: *n*-butyllithium 1.6 *M* (1.7 mL, 2.7 mmol, 3.2 equiv.), di*iso*propylamine (0.38 mL, 2.8 mmol, 3.8 equiv.). t_1 = 30 min, t_2 = 1.5 h. Electrophile: acetaldehyde (1 mL). The eluent for chromatography was a mixture of cyclohexane/ethyl acetate (90/10). Compound **12a** was obtained as a colorless oil (56 mg, 20 %). ^{1}H NMR ($CDCl_3$): δ = 8.64 (s, 1H, H_6); 5.16 (m, 1H, CH); 2.69 (s, 1H, OH); 1.53 (d, 3H, J_{CH} = 6.4 Hz CH_3). ^{13}C NMR: δ = 157.8 (C_6); 152.3 (C_4); 149.9 (C_2); 139.1 (C_5); 66.8 (CH); 23.7 (CH_3). IR (cm^{-1}): 3399; 2977; 2928; 1548; 1514; 1370; 1225; 1154; 1117; 1068; 820; 764; 696. M.S. (EI) m/z: 284 (M^+ + 2), 5); 282 ((M^+)), 10); 280 ((M^+ – 2), 5); 269 (48); 267 (97); 265 (48); 187 (25); 185 (25).

2,4-Dibromo-6-(1-hydroxyethyl)pyrimidine (**12b**).

Metalation of 2,4-dibromopyrimidine **2** (0,2 g, 0.84 mmol) following the general procedure. V_1(THF) = 7 ml; T = -100 °C; LTMP: *n*-butyllithium 1.6 *M* (1.7 mL, 2.7 mmol, 3.2 equiv.), 2,2,6,6-tetramethylpiperidine (0.47 mL, 2.8 mmol, 3.3 equiv.). t_1 = 30 min, t_2 = 1,5 h. Electrophile: acetaldehyde (1 mL). The eluent for chromatography was a mixture *n*-heptane/ethylacetate (80/20). Compound **12b** was obtained as a colorless oil (59 mg, 21 %). ^{1}H NMR ($CDCl_3$): δ (ppm) = 7.66 (s, 1H, H_5); 4.84 (q, 1H, J = 6.4 Hz, CH); 2.89 (s, 1H, OH); 1.53 (d, 3H, J_{CH} = 6.4 Hz, CH_3). ^{13}C NMR: δ (ppm) = 176.5 (C_6); 153.9 (C_4); 151.2 (C_2); 120.5 (C_5); 69.1 (CH); 23.6 (CH_3). IR (cm^{-1}): 3377; 2971; 2926; 1555; 1514; 1321; 1296; 1226;1075; 872; 837; 780; 658. M.S. (EI) m/z: 284 ((M^+ + 2), 3); 282 ((M^+), 6); 280 ((M^+ – 2), 3); 269 (35); 267 (70); 265 (50); 187 (16); 159 (40); 157 (40).

2,4-Dibromo-5-(1-hydroxy-*p*-methoxyphenylmethyl)pyrimidine (**13a**).

Metalation of 2,4-dibromopyridine **2** (0.23 g, 0.96 mmol) following the general procedure. V_1(THF) = 5 ml; T = -100 °C; LDA: *n*-butyllithium 1.6 *M* (1.8 mL, 2.9 mmol, 3.2 equiv.), di*iso*propylamine (0.45 mL, 3.2 mmol, 3.3 equiv.). t_1 = 30 min, t_2 = 1.5 h. Electrophile: *p*-methoxybenzaldehyde (0.38 mL, 2.9 mmol, 3.2 equiv.). The eluent for chromatography was a mixture dichloromethane/ethylacetate (98/2). Compound **13a** was obtained as a white solid (94 mg, 26 %). mp 112-4 °C. ^{1}H NMR: δ (ppm) = 8.75 (s, 1H, H_6); 7.26 (d, 2H, J = 8.7, H_{Ph}); 6.88 (d, 2H, J = 8.7, H_{Ph}); 5.92 (s, 1H, CH); 3.80 (s, 3H, OCH_3); 2.65 (s, 1H, OH). ^{13}C NMR: δ (ppm) = 160.0 ($C_{Ph,\ OMe}$); 158.1 (C_6); 153.2 (C_4); 150.1 (C_2); 137.1 (C_5); 132 (C_{Ph}); 128.8 (C_{Ph}); 114.5 (C_{Ph}); 72.5 (CH); 55.8 (OCH_3). IR (cm^{-1}): 3448, 2918, 2838, 1610, 1544, 1513, 1382, 1253, 1224, 1174, 1153, 1023, 813, 776. M.S. (EI) m/z: 376 ((M^+ + 2), 1); 374 ((M^+), 2); 372 ((M^+ – 2), 1); 360 (5); 358 (10); 356 (5); 345 (4); 348 (8); 341 (4); 137 (100); 121 (40); 77 (29).

2,4-Dibromo-6-(1-hydroxy-*p*-methoxyphenylmethyl)pyrimidine (**13b**).

Metalation of 2,4-dibromopyrimidine **2** (0.23 g, 0.96 mmol) following the general procedure V_1(THF) = 5 ml; T = -100 °C.

LTMP *n*-butyllithium 1.6 *M* (1.9 mL, 3.1 mmol, 3.2 equiv.), 2,2,6,6-tetramethylpiperidine (0.54 mL, 3.2 mmol, 3.3 equiv.). t_1 = 30 min, t_2 = 1,5 h. Electrophile *p*-methoxybenzylaldehyde (0.38 mL, 3.1 mmol, 3.2 equiv.). The eluent for chromatography was a mixture: dichloromethane/ethylacetate (96/14). **13b** was obtained as white solid (86 mg, 24 %). mp 106-8°C. ^{1}H NMR: δ (ppm) = 7.57 (s, 1H, H_5); 7.28 (d, 2H, J = 8.7 Hz, H_{Ph}); 6.89 (d, 2H, J = 8.7 Hz, H_{Ph}); 5.65 (s, 1H, CH); 3.80 (s, 3H, OCH_3); 3.61 (s, 1H, OH). ^{13}C NMR: δ (ppm) = 174.5 (C_6); 160.0 (C_{PhOMe}); 153.7 (C_4); 151 (C_2); 132.3 (C_{Ph}); 128.4 (C_{Ph}); 121.1 (C_5); 114.5 (C_{Ph}); 74.6 (CH); 55.4 (OCH_3). M.S. (EI) m/z: 376 ((M^+ + 2), 10); 374 ((M^+), 20); 372 ((M^+ – 2), 10); 360 (12); 358 (25); 356 (15); 343 (15); 341 (10); 240 (10); 238 (20); 236 (15); 137 (96); 121 (50); 77 (55).

3-Bromo-4-(1-hydroxy-*p*-methoxyphenylmethyl)-6-phenylpyridazine (**14**).

Metalation of 3-bromo-6-phenylpyrazine **7** (0,3 g, 1.28 mol) following the general procedure. V_1(THF) = 15 ml; T = -100 °C. LDA: *n*-butyllithium 1.6 *M* (1.8 mL, 2.93 mmol, 2.3 equiv.), di*iso*propylamine (0.41 mL, 2.81 mmol, 2.2 equiv.). t_1 = 30 min, t_2 = 1.5 h. Electrophile: *p*-methoxybenzylaldehyde (0.34 mL, 2.93 mmol, 2.3 equiv.). **14** was obtained as a white solid (0.40 g, 84 %). mp 164-166 °C. ^{1}H NMR (DMSO-d_6): δ (ppm) = 8.42 (s, 1H, H_5); 8.17 (m, 2H, H_{Ph}); 7.59 (m, 3H, H_{Ph}); 7.32 (d, 2H, J = 8.5 Hz, H_{PhOMe}); 6.89 (d, 2H, J = 8.5 Hz, H_{PhOMe}); 6.42 (d, 1H, J_{CHOH} = 4.3 Hz, OH); 5.78 (d, 1H, J_{CHOH} = 4.3 Hz, CH); 3.72 (s, 3H, OCH_3). ^{13}C NMR: δ (ppm) = 158.9 (C_{PhOMe}); 158.8 (C_6); 147.4 (C_4); 146.4 (C_3); 135 (C_{Ph}); 132.8 (C_{PhOMe}); 130.6 (CPh); 129.3 ($C_{Ph\ +\ PhOMe}$); 127.1 (C_{Ph}); 123.4 (C_5); 113.8 (C_{PhOMe}); 71.8 (CH); 55.1 (OCH_3). IR (cm^{-1}) = 3222; 3053; 2927; 1609; 1510; 1378; 1252; 1170; 1032; 835; 760; 697; 576.

Anal. Calcd. for $C_{18}H_{15}BrN_2O_2$ (371.24): C, 58.24; H, 4.07; N, 7.54. Found: C, 58.22; H, 4.24; N, 7.44.

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