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First Study of Syntheses and Reactivity of Grignard Compounds in the Diazine Series. Diazines. Part 27

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Abstract—A preparation of Grignard derivatives of diazines is described using a halogen magnesium exchange reaction. This convenient method allows the functionalization of these rings at 0°C or even room temperature.

Introduction

After some years of extensive research into lithio derivatives of diazines, it was established that they are very powerful tools for the syntheses of such heterocycles. Their main drawback are that they are generally only stable at very low temperature (<-50°C). A possible solution to this problem is to use other organometallic derivatives. We have recently tested organozinc derivatives,[1] which were useful for cross coupling reactions, but they were poorly reactive with other important electrophiles. We describe here the first convenient syntheses and reactivity of Grignard compounds of diazines.

In the literature only two publications report the use of a diazinic Grignard reagent. The first by Langley[2] in 1956 who prepared a carboxylic acid of pyrimidine via direct insertion of magnesium on a bromopyrimidine at low temperature (-70°C). More recently Yokoama[3] synthesized Grignard derivatives from bromopyrimidines using an exchange reaction with ethylmagnesium chloride. All these reports investigated only pyrimidine derivatives, so we developed a general method to prepare Grignard derivatives of all diazines: pyridazine, pyrimidine and pyrazine.

It has been highlighted[4–6] that good synthetic results were obtained using an exchange reaction between halo-pyridines and iso-propylmagnesium chloride. We wish to describe a similar approach in the diazine series. The syntheses and reaction of Grignard reagents of diazines with electrophiles are described.

Keywords: Grignard reactions/reagents; pyrazines; pyridazines; pyrimidines.

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Discussion

In the pyridazine series, the 3,6-dimethoxy-4-iodopyridazine **1** was easily prepared[7] and was used to establish the optimal experimental conditions (Scheme 1, Table 1).

A first attempt with 1.1 equiv. of PhMgBr afforded only the starting material, regardless of temperature and reaction time (entries 1, 2). The most efficient metallation conditions were obtained using 2 equiv. of PhMgBr at room temperature with a reaction time of 30 min (entry 3). On the contrary, for *i*-PrMgCl or *n*-BuMgCl, a quasi-stoichiometric amount was sufficient to obtain the magnesium derivative **2** with yields of 70–71% (entries 4, 7). Note that an excess of *i*-PrMgCl or *n*-BuMgCl led to an important degradation of the magnesium derivative **2** (entries 5, 8). Only half of a molar equivalent of di-*n*-butylmagnesium was necessary to obtain, after deuteriolysis, the deuteriated product **4** with a yield of 72% (entry 9). One equivalent of *n*-Bu_2Mg led to an important degradation (entry 10). The use of ether as a solvent (entry 6) produced lower yields. This could be explained by the low solubility of the iodo derivative in this solvent. Using the experimental conditions described above, some electrophiles have been tested on the magnesium derivative **2**, allowing synthesis of various trisubstituted pyridazines (Scheme 2, Table 2).

As previously observed, the same yields were obtained with 1 equiv. of *i*-PrMgCl or with 2 equiv. of PhMgBr (entries 1, 2). With a highly enolizable electrophile such as acetaldehyde, an important amount of compound **3** was observed (entry 3). This results from protonation of the magnesium derivative **2**. With less reactive electrophiles such as ethyl cyanoformate, *N*,*N*-dimethylformamide (DMF) or phenyl sulfide, moderate yields were observed (entries 6–8). Ethyl formate was unsuccessful for the preparation of the formyl derivative **10**, only compound **3** was obtained.

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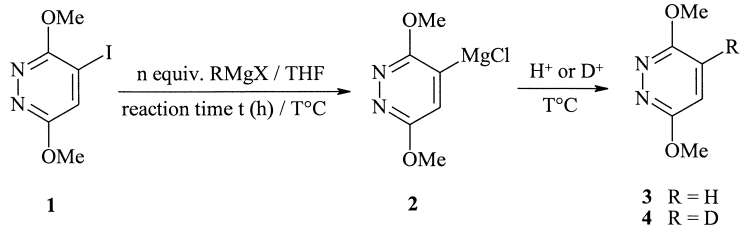
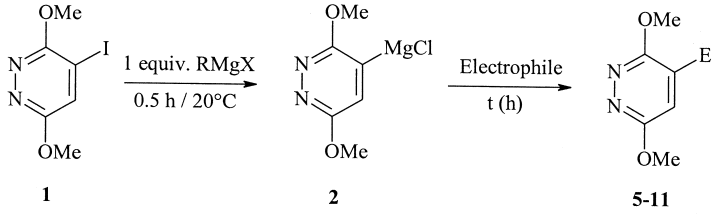


Scheme 1.

Table 1. Determination of optimal experimental conditions

Entry	RMgX	*n* equiv.	*t* (h)	*T* (°C)	Hydrolysis	Prod.	Yield (%)
1	PhMgBr	1.1	1	−40	H_2O	**3**	0[a]
2	PhMgBr	1.1	0.5	20	H_2O	**3**	0[a]
3	PhMgBr	2.0	0.5	20	DCl, EtOD	**4**	71
4	*i*-PrMgCl	1.1	0.5	20	DCl, EtOD	**4**	71
5	*i*-PrMgCl	2.0	0.5	20	DCl, EtOD	**3**	14
6	*i*-PrMgCl	1.1	1	20	CH_3OD	**4**	62[b]
7	*n*-BuMgCl	1.1	0.5	20	DCl, EtOD	**4**	70
8	*n*-BuMgCl	2.0	0.5	20	DCl, EtOD	**4**	0
9	*n*-Bu_2Mg	0.5	0.5	20	DCl, EtOD	**4**	72
10	*n*-Bu_2Mg	1.1	0.5	20	DCl, EtOD	**4**	0

[a] Starting material **1** was recovered quantitatively.
[b] This experiment was performed in ether, 15% of starting material **1** was recovered.

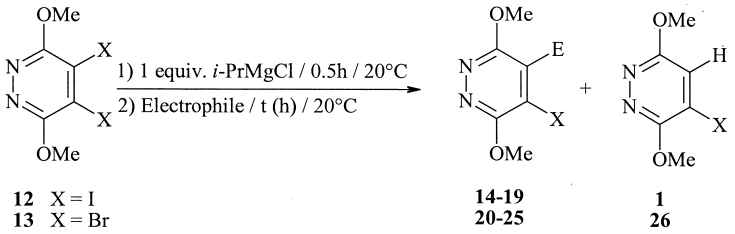


Scheme 2.

Table 2. Synthesis of trisubstituted pyridazines

Entry	RMgX	Electrophile	*t* (h)	E	Prod.	Yield (%)
1	PhMgBr	PhCHO	1	PhCH(OH)	**5**	70[a]
2	*i*-PrMgCl	PhCHO	1	PhCH(OH)	**5**	73
3	*i*-PrMgCl	CH_3CHO	1	$CH_3CH(OH)$	**6**	35[b]
4	*i*-PrMgCl	$C_5H_{11}CHO$	2	$C_5H_{11}CH(OH)$	**7**	69
5	*i*-PrMgCl	TMSCl	1	TMS–	**8**	41[c]
6	*i*-PrMgCl	NC–COOEt	1	EtOOC–	**9**	47[d]
7	*i*-PrMgCl	DMF	2	–CHO	**10**	42
8	*i*-PrMgCl	PhSSPh	12	PhS–	**11**	42

[a] Two equivalents of PhMgBr were used.
[b] The product **3** resulting from hydrolysis was obtained with yield of 49%.
[c] The product **3** resulting from hydrolysis was obtained with yield of 28%.
[d] The product **3** resulting from hydrolysis was obtained with yield of 5%.

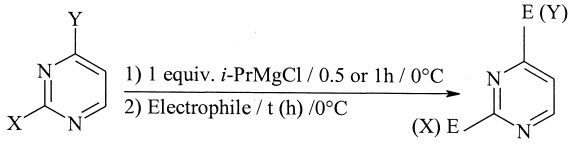


Scheme 3.

Table 3. Synthesis of tetrasubstituted pyridazines from dihalogeno derivatives

Entry	X	Electrophile	*t* (h)	E	Prod.	Yield (%)
1	I	PhCHO	1	PhCH(OH)	**14**	48[a]
2	I	PhCHO	2	PhCH(OH)	**14**	75
3	I	CH_3CHO	1	$CH_3CH(OH)$	–	0[b]
4	I	$C_5H_{11}CHO$	2	$C_5H_{11}CH(OH)$	**15**	74
5	I	TMSCl	1	TMS–	**16**	70
6	I	NC–COOEt	1	EtOOC–	**17**	30[c]
7	I	PhSSPh	12	PhS–	**18**	40
8	I	DMF	2	–CHO	**19**[d]	38
9	Br	H_2O	0.5	–H	**26**	80
10	Br	EtOD	0.5	–D	**20**	80
11	Br	PhCHO	2	PhCH(OH)	**21**	65
12	Br	$C_5H_{11}CHO$	2	$C_5H_{11}CH(OH)$	**22**	60
13	Br	NC–COOEt	12	EtOOC–	**23**	50
14	Br	I_2	2	–I	**25**	80
15	Br	DMF	2	–CHO	**19**[d]	47

[a] The product **1** resulting from hydrolysis was obtained with yield of 27%.
[b] The product **1** resulting from hydrolysis was obtained with yield of 45%.
[c] The product **1** resulting from hydrolysis was obtained with yield of 5%.
[d] 3,6-Dimethoxy-5-(*N*,*N*-dimethylamino)-4-formylpyridazine.



27 X = I Y = OCH_3 **28-30**
31 X = SCH_3 Y = I **32-35**

Scheme 4.

The same reaction was performed with 4,5-diiodo-3,6-dimethoxypyridazine **12** and 4,5-dibromo-3,6-dimethoxypyridazine **13** (Scheme 3, Table 3).

Starting from the bromo- or the iodo-derivative, using the same experimental conditions, the yields were approximately the same (compare entries 2 and 11, 4 and 12, 7 and 14). These results indicated that the nature of the halogen was not important. Formation of compound **1** results from protonation that can be explained in two ways: the reaction of the magnesium derivative with the electrophile was incomplete leading to the compound **1** after hydrolysis (entries 1, 6) or the abstraction of the hydrogen atom of an enolizable aldehyde could occur producing the compound **1** before hydrolysis (entry 3). When DMF was used as a formylating agent, a subsequent nucleophilic substitution of the remaining halogen atom by the dimethylamino moiety of the DMF was observed, leading to compound **19**.

In the pyrimidine series, two derivatives **27** and **31** were tested using the same experimental conditions at 0°C (Scheme 4, Table 4).

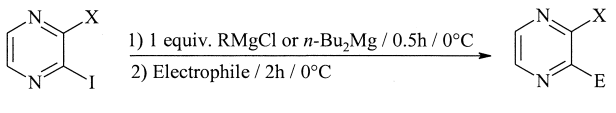
The iodine–magnesium exchange reaction with compound **27** was slower (1 h) than with compound **31** (0.5 h). The formation of the carbanionic species at the 2-position in the pyrimidine ring may be more difficult than at the 4-position. This may be due to the repulsive effect of the two unshared nitrogen electron pairs on the pyrimidine nucleus. However, once the magnesium derivatives of these pyrimidines were prepared, their reactivity toward aldehydes was comparable (compare entries 2 and 6, 3 and 7). When DMF was used as the electrophile, no formyl compound was obtained with compound **27**; whereas with compound **31** 2-methylsulfanyl-4-formylpyrimidine **35** was obtained with a moderate yield (34%).

In the pyrazine series four compounds were tested: 2-iodopyrazine **36**, 2-iodo-3-methoxypyrazine **37**, 2-chloro-3-iodopyrazine **38** and 2,3-diiodopyrazine **39** (Scheme 5, Table 5).

In the case of compound **36**, it was not possible to use *i*-PrMgCl or PhMgBr, even at low temperatures (−70 or −40°C), this should be due to a greater sensitivity of the diazine rings to nucleophilic attacks.[3] Consequently, *n*-BuMgCl, which is known to be less nucleophilic than *i*-PrMgCl, was used successfully. Compound **37** bearing a methoxy group is less readily attacked by nucleophiles. So it could be reacted with *i*-PrMgCl to give the Grignard derivative which, reacted with electrophiles, afforded yields higher than 50%. The 3-chloro-2-iodopyrazine **38** is sensitive to nucleophilic attack, so *n*-BuMgCl was used. The reaction with benzaldehyde as the electrophile produced yields only of 24% at 0°C (entry 6). It was supposed that this low yield was due to a low stability of the Grignard derivative and the same reaction was performed at −70°C but the yield was only slightly increased (entry 7). However, our aim was to achieve functionalization of the diazine derivatives at a more convenient temperature (0 or 20°C). From the previously performed studies in the pyridine series,[8] it has been shown that the addition of 1 equiv. of triethylamine to the Grignard reagent could improve the yields. From this work we assume that triethylamine stabilized the organometallic derivative and consequently enhanced its reactivity. The reaction performed with *n*-BuMgCl and 1 equiv. of triethylamine produced the

Table 4. Synthesis of disubstituted pyrimidines

Entry	Starting material	Electrophile	*t* (h)	E	Prod.	Yield (%)
1	**27**	PhCHO	1	PhCH(OH)	**28**	57
2	**27**	PhCHO	2	PhCH(OH)	**28**	69
3	**27**	$C_5H_{11}CHO$	2	$C_5H_{11}CH(OH)$	**29**	64
4	**27**	NC–COOEt	12	EtOOC–	**30**	60
5	**31**	PhCHO	1	PhCH(OH)	**32**	27
6	**31**	PhCHO	2	PhCH(OH)	**32**	57
7	**31**	$C_5H_{11}CHO$	2	$C_5H_{11}CH(OH)$	**33**	55
8	**31**	NC–COOEt	12	EtOOC–	**34**	35
9	**31**	DMF	2	–CHO	**35**	34



36 X = H
37 OCH_3
38 Cl
39 I

40-41
42-44
45-46
47

Scheme 5.

same yield as the reaction performed without the amine at −70°C (compare entries 6 and 8). The use of the couple *n*-Bu_2Mg/triethylamine gave the best result: a 44% yield was obtained. The diiodo compound **39** produced a very low yield and no optimization experiments were performed.

Conclusion

In summary, we have demonstrated that it was possible to prepare Grignard reagents of diazines using an efficient and reproducible method. These compounds were stable at a convenient temperature (>0°C) and reacted with electrophiles with acceptable yields. In some cases, when the diazine rings did not bear a methoxy or a methylsulfanyl group, we proposed some different exchange reactants and even an additive that allowed yield enhancement.

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. 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.

Tetrahydrofuran was distilled from benzophenone/sodium solution and used immediately. Water content of the solvent was estimated by the modified Karl Fischer method (THF less than 50 ppm water). Reactions were performed under an argon atmosphere. Reagents were handled with syringes through septa.

PhMgBr (1 M in THF), *i*-PrMgCl (2 M in THF), *n*-BuMgCl (2 M in THF), *n*-Bu_2Mg (1 M in heptane) were purchased from Aldrich Chemical Co. or Acros.

The following diazines were synthesized according to the literature: 2-iodopyrazine **36**,[9] 2,3-diiodopyrazine **39**,[9] 2-iodo-3-methoxypyrazine **37**,[10] 2-chloro-3-iodopyrazine **38**,[11] 4-iodo-2-methylsulfanylpyrimidine **31**,[9] 3,6-dimethoxypyridazine **3**[7] and 4-iodo-3,6-dimethoxypyridazine **1**.[7]

General procedure for metalation reaction

A solution of *n*-butyllithium (1.6 or 2.5 M in hexane) was added to cold (−50°C), anhydrous THF under an atmosphere of dry argon, 2,2,6,6-tetramethylpiperidine was then added. The mixture was stirred at 0°C for 20 min. The mixture temperature was then lowered to −70°C. A solution of diazine in THF (5 mL) was added and the mixture was stirred for a time t_1 at a temperature T_1. The electrophile was introduced and stirring was continued for a time t_2 at T_2. Hydrolysis was then carried out using a solution of ethanol (3 mL) and THF (5 mL) at −70°C. The solution was warmed to room temperature. When the electrophile was iodine, the solution was decolorized with sodium thiosulphate and evaporated nearly to dryness. **Caution:** When the electrophile was cyanogen bromide, the reaction medium was made basic with a solution of sodium hydroxide (2 M) and cyanide ions were decomposed with a concentrated solution of sodium hypochlorite. The residue was extracted with dichloromethane (3×15 mL). The organic layer was dried over magnesium sulfate and evaporated. The crude product was purified by column chromatography on silica gel.

General procedure for exchange reaction

The diazine derivative (1 mmol) dissolved in 3 mL of THF was stirred and cooled to 0°C under an atmosphere of dry argon. The magnesium reagent was added slowly. Then the reaction mixture was allowed to stand at T_1 for a time t_1. The electrophile was introduced and stirring was continued for a time t_2 at T_2. Hydrolysis was then carried out using an aqueous saturated solution of sodium chloride or ammonium chloride when the expected product was an alcohol. The aqueous layer was extracted with dichloromethane (3×15 mL). The organic layer was dried over magnesium

Table 5. Synthesis of pyrazine derivatives

Entry	Starting material	RMgX	Electrophile	E	Prod.	Yield (%)
1	**36**	*n*-BuMgCl	PhCHO	PhCH(OH)	**40**	59
2	**36**	*n*-BuMgCl	$C_5H_{11}CHO$	$C_5H_{11}CH(OH)$	**41**	33
3	**37**	*i*-PrMgCl	$C_5H_{11}CHO$	PhCH(OH)	**42**	56
4	**37**	*i*-PrMgCl	$C_5H_{11}CHO$	$C_5H_{11}CH(OH)$	**43**	50
5	**37**	*i*-PrMgCl	DMF	−CHO	**44**	51
6	**38**	*n*-BuMgCl	PhCHO	PhCH(OH)	**45**	24
7	**38**	*n*-BuMgCl	PhCHO	PhCH(OH)	**45**	32[a]
8	**38**	*n*-BuMgCl, NEt_3	PhCHO	PhCH(OH)	**45**	33
9	**38**	*n*-Bu_2Mg	PhCHO	PhCH(OH)	**45**	37
10	**38**	*n*-Bu_2Mg, NEt_3	PhCHO	PhCH(OH)	**45**	44
11	**38**	*n*-BuMgCl	$C_5H_{11}CHO$	$C_5H_{11}CH(OH)$	**46**	20
12	**39**	*n*-BuMgCl	PhCHO	PhCH(OH)	**47**	11

[a] Reaction performed at −70 °C.

sulfate and evaporated. The crude product was purified by column chromatography on silica gel.

4-Deuterio-3,6-dimethoxypyridazine (4). Exchange reaction of **1** (266 mg, 1.0 mmol) according to the general procedure with *i*-PrMgCl 2.0 M (1 equiv., 0.5 mL), t_1=30 min, T_1=20°C, followed by deuteriolysis with DCl, EtOD (1 mL), t_2=15 min, T_2=20°C, gave after purification by column chromatography (silica, eluent: dichloromethane) 100 mg (71%) of **4** as a white solid, mp 107°C; ^{1}H NMR ($CDCl_3$): δ 6.95 (s, 1H, H_5); 4.05 (s, 6H, 2×OCH_3); ^{13}C NMR ($CDCl_3$): δ 162.3; 121.7; 54.9. Anal. Calcd for $C_6H_7N_2O_2D$ (141.15): C, 51.06; H, 5.00; N, 19.85. Found: C, 51.25; H, 4.78; N, 19.95.

3,6-Dimethoxy-4-hydroxybenzylpyridazine (5). Exchange reaction of **1** (266 mg, 1.0 mmol) according to the general procedure with *i*-PrMgCl 2.0 M (1 equiv., 0.5 mL), t_1=30 min, T_1=20°C, followed by reaction with benzaldehyde (0.11 mL, 1.1 mmol), t_2=1 h, T_2=20°C, gave after purification by column chromatography (silica, eluent: dichloromethane) 180 mg (73%) of **5** as a white solid, mp 102°C, lit.=99–101°C; ^{1}H NMR ($CDCl_3$): δ 7.25 (m, 5H, H_{Ph}); 7.15 (s, 1H, H_5); 5.75 (s, 1H, CH); 4.05 (s, 3H, OCH_3); 4.00 (s, 3H, OCH_3); 3.70 (br, 1H, OH); IR: ν 3300, 3030, 3000, 2960, 2900, 1630, 1500, 1475, 1460, 1390, 1265, 1220, 1140 cm^{-1}. Anal. Calcd for $C_{13}H_{14}N_2O_3$ (246.27): C, 63.40; H, 5.73; N, 11.38. Found: C, 63.53; H, 5.80; N, 11.22.

3,6-Dimethoxy-4-(1-hydroxy)ethylpyridazine (6). Exchange reaction of **1** (266 mg, 1.0 mmol) according to the general procedure with *i*-PrMgCl 2.0 M (1 equiv., 0.5 mL), t_1=30 min, T_1=20°C, followed by reaction with acetaldehyde (2 mL), t_2=1 h, T_2=20°C, gave after purification by column chromatography (silica, eluent: dichloromethane) 64 mg (35%) of **6** as a white solid, mp 84°C; ^{1}H NMR ($CDCl_3$): δ 7.10 (s, 1H, H_5); 5.00 (q, J=6.0 Hz, 1H, CH); 4.05 (s, 3H, OCH_3); 4.00 (s, 3H, OCH_3); 3.50 (br, 1H, OH); 1.50 (d, J=6.0 Hz, 3H, CH_3); IR: ν 3300, 3020, 2980, 2960, 1630, 1475, 1380, 1280, 1235, 1155, 1095, 1020, 1010 cm^{-1}. Anal. Calcd for $C_8H_{12}N_2O_3$ (184.20): C, 52.17; H, 6.57; N, 15.21. Found: C, 51.95; H, 6.40; N, 15.34.

3,6-Dimethoxy-4-(1-hydroxy)hexylpyridazine (7). Exchange reaction of **1** (266 mg, 1.0 mmol) according to the general procedure with *i*-PrMgCl 2.0 M (1 equiv., 0.5 mL), t_1=30 min, T_1=20°C, followed by reaction with hexanal (0.13 mL, 1.1 mmol), t_2=2 h, T_2=20°C, gave after purification by column chromatography (silica, eluent: dichloromethane) 166 mg (69%) of **7** as a yellow oil; ^{1}H NMR ($CDCl_3$): δ 7.00 (s, 1H, H_5); 4.75 (m, 1H, CH); 4.02 (s, 3H, OCH_3); 3.99 (s, 3H, OCH_3); 3.25 (br, 1H, OH); 2.27 (m, 1H, CH); 1.60 (m, 1H, CH); 1.27 (m, 6H, 3×CH_2); 0.86 (m, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 163.1; 160.9; 139.6; 121.8; 68.2; 54.8; 54.7; 36.5; 31.6; 25.7; 23.0; 14.3; IR: ν 3368, 2930, 2860, 1469, 1385, 1014 cm^{-1}. Anal. Calcd for $C_{12}H_{20}N_2O_3$ (240.30): C, 59.98; H, 8.39; N, 11.66. Found: C, 59.75; H, 8.43; N, 11.33.

3,6-Dimethoxy-4-trimethylsilylpyridazine (8). Exchange reaction of **1** (266 mg, 1.0 mmol) according to the general procedure with *i*-PrMgCl 2.0 M (1 equiv., 0.5 mL), t_1=30 min, T_1=20°C, followed by reaction with trimethylsilyl chloride (0.14 mL, 1.1 mmol), t_2=1 h, T_2=20°C, gave after purification by column chromatography (silica, eluent: dichloromethane) 87 mg (41%) of **8** as a red solid, mp <50°C; ^{1}H NMR ($CDCl_3$): δ 6.90 (s, 1H, H_5); 4.00 (s, 6H, 2×OCH_3); 0.10 (s, 9H, $SiMe_3$); ^{13}C NMR ($CDCl_3$): δ 166.9; 164.0; 137.0; 129.1; 56.9; 0.0; IR: ν 3352, 2952, 1727, 1462, 1368, 1242, 1013, 843, 701 cm^{-1}. Anal. Calcd for $C_9H_{16}N_2O_2Si$ (212.33): C, 50.91; H, 7.60; N, 13.19. Found: C, 50.82; H, 7.72; N, 13.09.

Ethyl-3,6-dimethoxypyridazine-4-carboxylate (9). Exchange reaction of **1** (266 mg, 1.0 mmol) according to the general procedure with *i*-PrMgCl 2.0 M (1 equiv., 0.5 mL), t_1=30 min, T_1=20°C, followed by reaction with ethyl cyanoformate (0.11 mL, 1.1 mmol), t_2=1 h, T_2=20°C, gave after purification by column chromatography (silica, eluent: dichloromethane) 100 mg (47%) of **9** as a white solid, mp 148–149°C; ^{1}H NMR ($CDCl_3$): δ 7.41 (s, 1H, H_5); 4.38 (q, J=4.8 Hz, 2H, CH_2); 4.02 (s, 3H, OCH_3); 3.99 (s, 3H, OCH_3); 1.34 (t, J=4.8 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 161.6; 160.4; 131.2; 121.8; 94.4; 63.3; 56.3; 55.7; 14.4; IR: ν 2950, 2864, 1743, 1578, 1467, 1363, 1265, 1228, 1007, 896, 855, 772 cm^{-1}. Anal. Calcd for $C_9H_{12}N_2O_4$ (212.21): C, 50.94; H, 5.70; N, 13.20. Found: C, 51.22; H, 5.88; N, 13.08.

3,6-Dimethoxy-4-formylpyridazine (10). Exchange reaction of **1** (266 mg, 1.0 mmol) according to the general procedure with *i*-PrMgCl 2.0 M (1 equiv., 0.5 mL), t_1=30 min, T_1=20°C, followed by reaction with DMF (0.09 mL, 1.1 mmol), t_2=2 h, T_2=20°C, gave after purification by column chromatography (silica, eluent: dichloromethane) 71 mg (42%) of **10** as a yellow solid, mp 84°C; ^{1}H NMR ($CDCl_3$): δ 10.3 (s, 1H, CHO); 7.3 (s, 1H, H_5); 4.20 (s, 3H, OCH_3); 4.05 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$): δ 188.7; 163.4; 160.3; 125.4; 118.4; 55.5; IR: ν 3380, 3068, 2998, 2958, 2885, 1702, 1618, 1473, 1451, 1383, 1321, 1238, 1145, 1024, 1008, 991, 940, 920, 764 cm^{-1}. Anal. Calcd for $C_7H_8N_2O_3$ (168.15): C, 50.00; H, 4.80; N, 16.66. Found: C, 49.78; H, 4.83; N, 16.89.

3,6-Dimethoxy-4-phenylsulfanylpyridazine (11). Exchange reaction of **1** (266 mg, 1.0 mmol) according to the general procedure with *i*-PrMgCl 2.0 M (1 equiv., 0.5 mL), t_1=30 min, T_1=20°C, followed by reaction with phenyl sulfide (242 mg, 1.1 mmol), t_2=12 h, T_2=20°C, gave after purification by column chromatography (silica, eluent: dichloromethane) 104 mg (42%) of **11** as an orange oil; ^{1}H NMR ($CDCl_3$): δ 7.5 (m, 5H, H_{Ph}); 7.2 (s, 1H, H_5); 4.10 (s, 3H, OCH_3); 3.95 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$): δ 162.5; 157.9; 138.3; 136.3; 130.8; 127.5; 124.0, 114.1; 55.5; 54.8; IR: ν 2948, 2864, 1581, 1466, 1382, 1234, 1029, 1011 cm^{-1}. Anal. Calcd for $C_{12}H_{12}N_2O_2S$ (248.31): C, 58.05; H, 4.87; N, 11.28. Found: C, 58.25; H, 4.65; N, 11.02.

4,5-Diiodo-3,6-dimethoxypyridazine (12). Metallation of **3** (700 mg, 5.0 mmol) according to the general procedure with *n*-BuLi 1.6 M (7.2 mL, 11.5 mmol), TMPH (1.9 mL, 11.5 mmol), V=75 mL, t_1=1 h, T_1=−70°C, followed by reaction with iodine (3.0 g, 11.8 mmol), t_2=1 h 30 min,

T_2=−70°C, gave after purification by column chromatography (silica, eluent: petroleum ether/ethylacetate (9/1)) 1.49 g (76%) of **12** as a white solid, mp 192°C; ^{1}H NMR ($CDCl_3$): δ 4.01 (s, OCH_3); ^{13}C NMR ($CDCl_3$): δ 160.5; 152.7; 56.9; IR: ν 2984, 2941, 2854, 1527, 1460, 1343, 1190, 1008, 865, 780, 653 cm^{-1}. MS: $(M)^{+\cdot}$, 392. Anal. Calcd for $C_6H_6I_2N_2O_2$ (391.94): C, 18.39; H, 1.54; N, 7.15. Found: C, 18.26; H, 1.60; N, 7.22.

4,5-Dibromo-3,6-dimethoxypyridazine (13). Metallation of **3** (700 mg, 5.0 mmol) according to the general procedure with *n*-BuLi 1.6 M (7.2 mL, 11.5 mmol), TMPH (1.9 mL, 11.5 mmol), V=75 mL, t_1=1 h, T_1=−70°C, followed by reaction with cyanogen bromide (1.5 g, 12.0 mmol), t_2=1 h 30 min, T_2=−70°C, gave after purification by column chromatography (silica, eluent: dichloromethane) 2.2 g (74%) of **13** as a white solid, mp 146–148°C; ^{1}H NMR ($CDCl_3$): δ 4.05 (s, OCH_3); ^{13}C NMR ($CDCl_3$): δ 161.3; 124.9; 58.6; IR: ν 3006, 2955, 2864, 1560, 1469, 1365, 1194, 1016, 882, 793, 659 cm^{-1}. Anal. Calcd for $C_6H_6Br_2N_2O_2$ (297.93): C, 24.19; H, 2.03; N, 9.40. Found: C, 24.10; H, 1.96; N, 9.68.

3,6-Dimethoxy-5-hydroxybenzyl-4-iodopyridazine (14). Exchange reaction of **12** (392 mg, 1.0 mmol) according to the general procedure with *i*-PrMgCl 2.0 M (1 equiv., 0.5 mL), t_1=30 min, T_1=20°C, followed by reaction with benzaldehyde (0.11 mL, 1.1 mmol), t_2=2 h, T_2=20°C, gave after purification by column chromatography (silica, eluent: dichloromethane) 279 mg (75%) of **14** as a yellow solid, mp 124–126°C; ^{1}H NMR ($CDCl_3$): δ 7.40 (m, 5H, H_{Ph}); 6.15 (d, J=11.0 Hz, 1H, CH); 5.00 (br, 1H, OH); 4.15 (s, 3H, OCH_3); 4.00 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$): δ 159.6; 157.3; 139.1; 137.9; 127.5; 126.8; 124.3; 98.1; 78.2; 55.2; 54.3; IR: ν 3512, 3234, 2949, 1461, 1366, 1274, 1004, 737, 714, 678 cm^{-1}. MS: $(M)^{+\cdot}$, 372. Anal. Calcd for $C_{13}H_{13}IN_2O_3$ (372.16): C, 41.96; H, 3.52; N, 7.53. Found: C, 42.14; H, 3.35; N, 7.68.

3,6-Dimethoxy-5-(1-hydroxy)hexyl-4-iodopyridazine (15). Exchange reaction of **12** (392 mg, 1.0 mmol) according to the general procedure with *i*-PrMgCl 2.0 M (1 equiv., 0.5 mL), t_1=30 min, T_1=20°C, followed by reaction with hexanal (0.13 mL, 1.1 mmol), t_2=2 h, T_2=20°C, gave after purification by column chromatography (silica, eluent: dichloromethane) 271 mg (74%) of **15** as a yellow oil; ^{1}H NMR ($CDCl_3$): δ 4.81 (m, 1H, CH); 4.00 (s, 3H, OCH_3); 3.95 (s, 3H, OCH_3); 3.52 (br, 1H, OH); 2.23 (m, 1H, CH); 1.55 (m, 1H, CH); 1.24 (m, 6H, 3×2CH_2); 0.82 (m, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 160.9; 158.7; 140.2; 98.0; 78.4; 56.5; 55.6; 35.8; 31.9; 25.7; 23.3; 14.3; IR: ν 3418, 2952, 2860, 1462, 1369, 1049, 1016 cm^{-1}. MS: $(M)^{+\cdot}$, 366. Anal. Calcd for $C_{12}H_{19}IN_2O_3$ (366.20): C, 39.36; H, 5.23; N, 7.65. Found: C, 39.52; H, 5.38; N, 7.57.

3,6-Dimethoxy-4-iodo-5-trimethylsilylpyridazine (16). Exchange reaction of **12** (392 mg, 1.0 mmol) according to the general procedure with *i*-PrMgCl 2.0 M (1 equiv., 0.5 mL), t_1=30 min, T_1=20°C, followed by reaction with trimethylsilyl chloride (0.14 mL, 1.1 mmol), t_2=1 h, T_2=20°C, gave after purification by column chromatography (silica, eluent: dichloromethane) 237 mg (70%) of **16** as a white solid, mp 55°C; ^{1}H NMR ($CDCl_3$): δ 4.00 (s, 3H, OCH_3); 3.95 (s, 3H, OCH_3); 0.40 (s, 9H, $SiMe_3$); ^{13}C NMR ($CDCl_3$): δ 161.9; 158.7; 129.3; 103.0; 55.1; 54.6; 0.0; IR: ν 2985, 2947, 2898, 1458, 1346, 1246, 1020, 877, 847, 772 cm^{-1}. Anal. Calcd for $C_9H_{15}IN_2O_2Si$ (338.22): C, 31.96; H, 4.47; N, 8.28. Found: C, 32.08; H, 4.61; N, 8.16.

Ethyl-3,6-dimethoxy-5-iodopyridazine-4-carboxylate (17). Exchange reaction of **12** (392 mg, 1.0 mmol) according to the general procedure with *i*-PrMgCl 2.0 M (1 equiv., 0.5 mL), t_1=30 min, T_1=20°C, followed by reaction with ethyl cyanoformate (0.11 mL, 1.1 mmol), t_2=1 h, T_2=20°C, gave after purification by column chromatography (silica, eluent: dichloromethane) 101 mg (30%) of **17** as a white solid, mp 98–100°C; ^{1}H NMR ($CDCl_3$): δ 4.41 (q, J=7.1 Hz, 2H, CH_2); 4.03 (s, 3H, OCH_3); 4.01 (s, 3H, OCH_3); 1.34 (t, J=7.1 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 164.0; 160.3; 157.3; 134.5; 93.1; 63.3; 56.6; 55.9; 14.4; IR: ν 2994, 2951, 2860, 1719, 1581, 1519, 1466, 1360, 1276, 1136, 1039, 1011, 768 cm^{-1}. MS: $(M)^{+\cdot}$, 338. Anal. Calcd for $C_9H_{11}IN_2O_4$ (338.10): C, 31.97; H, 3.28; N, 8.29. Found: C, 32.05; H, 3.08; N, 8.65.

3,6-Dimethoxy-4-iodo-5-phenylsulfanylpyridazine (18). Exchange reaction of **12** (392 mg, 1.0 mmol) according to the general procedure with *i*-PrMgCl 2.0 M (1 equiv., 0.5 mL), t_1=30 min, T_1=20 °C, followed by reaction with phenyl sulfide (242 mg, 1.1 mmol), t_2=12 h, T_2=20 °C, gave after purification by column chromatography (silica, eluent: dichloromethane) 150 mg (40%) of **19** as a yellow solid, mp 70–72°C; ^{1}H NMR ($CDCl_3$): δ 7.19 (s, 5H, H_{Ph}); 4.03 (s, 3H, OCH_3); 3.76 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$): δ 161.0; 159.6; 136.3; 133.3; 130.7; 129.5; 128.0; 104.9; 56.6; 55.8; IR: ν 3052, 2947, 1460, 1358, 1020, 791, 740, 662 cm^{-1}. Anal. Calcd for $C_{12}H_{11}IN_2O_2S$ (374.20): C, 38.52; H, 2.96; N, 7.49. Found: C, 38.69; H, 2.77; N, 7.55.

3,6-Dimethoxy-5-(*N*,*N*-dimethylamino)-4-formylpyridazine (19). Exchange reaction of **12** (392 mg, 1.0 mmol) according to the general procedure with *i*-PrMgCl 2.0 M (1 equiv., 0.5 mL), t_1=30 min, T_1=20 °C, followed by reaction with DMF (0.09 mL, 1.1 mmol), t_2=2 h, T_2=20 °C, gave after purification by column chromatography (silica, eluent: dichloromethane) 88 mg (38%) of **19** as a yellow solid, mp 115–116°C; ^{1}H NMR ($CDCl_3$): δ 10.08 (s, 1H, CHO); 3.99 (s, 3H, OCH_3); 3.96 (s, 3H, OCH_3); 3.02 (s, 6H, NMe_2); ^{13}C NMR ($CDCl_3$): δ 185.3; 160.9; 153.9; 139.4; 105.6; 52.9; 43.6; IR: ν 2975, 2947, 2887, 1664, 1553, 1462, 1407, 1390, 1346, 1315, 1178, 1091, 1064, 952, 769, 691 cm^{-1}. Anal. Calcd for $C_9H_{13}N_3O_3$ (211.22): C, 51.18; H, 6.20; N, 19.89. Found: C, 51.31; H, 6.11; N, 19.58.

4-Bromo-5-deuterio-3,6-dimethoxypyridazine (20). Exchange reaction of **13** (298 mg, 1.0 mmol) according to the general procedure with *i*-PrMgCl 2.0 M (1 equiv., 0.5 mL), t_1=30 min, T_1=20 °C, followed by hydrolysis with EtOD (1 mL), t_2=15 min, T_2=20 °C, gave after purification by column chromatography (silica, eluent: dichloromethane) 176 mg (80%) of **20** as a white solid, mp 74–76°C; ^{1}H NMR ($CDCl_3$): δ 4.04 (s, 3H, OCH_3); 3.96 (s, 3H, OCH_3); IR: ν 2988, 2952, 1589, 1462, 1370, 1230, 1061, 1026, 1006, 894, 774 cm^{-1}. Anal. Calcd for

$C_6H_6N_2O_2BrD$ (220.04): C, 32.75; H, 2.75; N, 12.73. Found: C, 32.64; H, 2.71; N, 12.58.

4-Bromo-3,6-dimethoxy-5-hydroxybenzylpyridazine (21). Exchange reaction of **13** (298 mg, 1.0 mmol) according to the general procedure with *i*-PrMgCl 2.0 M (1 equiv., 0.5 mL), t_1=30 min, T_1=20 °C, followed by reaction with benzaldehyde (0.11 mL, 1.1 mmol), t_2=2 h, T_2=20 °C, gave after purification by column chromatography (silica, eluent: dichloromethane) 211 mg (65%) of **21** as an orange solid, mp 92°C; ^{1}H NMR ($CDCl_3$): δ 7.25 (s, 5H, H_{Ph}); 6.25 (d, J=7.0 Hz, 1H, CH); 5.21 (d, J=7.0 Hz, 1H, OH); 4.06 (s, 3H, OCH_3); 3.95 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$): δ 159.7; 159.4; 140.5; 135.0; 128.9; 128.3; 125.7; 119.7; 73.6; 56.3; 55.8; IR: ν 3391, 2952, 1468, 1376, 1039, 1017, 776, 739, 715 cm^{-1}. Anal. Calcd for $C_{13}H_{13}BrN_2O_3$ (325.16): C, 48.02; H, 4.03; N, 8.62. Found: C, 48.18; H, 3.87; N, 8.51.

4-Bromo-3,6-dimethoxy-5-(1-hydroxy)hexylpyridazine (22). Exchange reaction of **13** (298 mg, 1.0 mmol) according to the general procedure with *i*-PrMgCl 2.0 M (1 equiv., 0.5 mL), t_1=30 min, T_1=20 °C, followed by reaction with hexanal (0.13 mL, 1.1 mmol), t_2=2 h, T_2=20 °C, gave after purification by column chromatography (silica, eluent: dichloromethane) 191 mg (60%) of **22** as a red solid, mp 94°C; ^{1}H NMR ($CDCl_3$): δ 5.00 (m, 1H, CH); 4.05 (s, 3H, OCH_3); 4.00 (s, 3H, OCH_3); 3.30 (br, 1H, OH); 1.80 (m, 1H, CH); 1.60 (m, 1H, CH); 1.15 (m, 6H, 3×CH_2); 0.90 (m, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 161.1; 159.8; 135.9; 118.6; 73.1; 56.2; 55.7; 36.0; 31.8; 25.6; 22.9; 14.4; IR: ν 3428, 2953, 2930, 2860, 1466, 1376, 1051, 1018 cm^{-1}. Anal. Calcd for $C_{12}H_{19}BrN_2O_3$ (319.20): C, 45.15; H, 6.00; N, 8.78. Found: C, 44.94; H, 5.87; N, 8.90.

Ethyl-5-bromo-3,6-dimethoxypyridazine-4-carboxylate (23). Exchange reaction of **13** (298 mg, 1.0 mmol) according to the general procedure with *i*-PrMgCl 2.0 M (1 equiv., 0.5 mL), t_1=30 min, T_1=20°C, followed by reaction with ethyl cyanoformate (0.11 mL, 1.1 mmol), t_2=12 h, T_2=20°C, gave after purification by column chromatography (silica, eluent: dichloromethane) 145 mg (50%) of **23** as a white solid, mp 64–65°C; ^{1}H NMR ($CDCl_3$): δ 4.37 (q, J=7.0 Hz, 2H, CH_2); 4.05 (s, 3H, OCH_3); 4.00 (s, 3H, OCH_3); 1.31 (t, J=7.0 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 162.6; 158.6; 157.8; 128.8; 116.7; 63.1; 56.2; 55.8; 14.3; IR: ν 2884, 2958, 1742, 1474, 1367, 1278, 1017, 766 cm^{-1}. Anal. Calcd for $C_9H_{11}BrN_2O_4$ (291.10): C, 37.13; H, 3.81; N, 9.62. Found: C, 37.38; H, 3.62; N, 9.78.

4-Bromo-3,6-dimethoxy-5-iodopyridazine (25). Exchange reaction of **13** (298 mg, 1.0 mmol) according to the general procedure with *i*-PrMgCl 2.0 M (1 equiv., 0.5 mL), t_1=30 min, T_1=20°C, followed by reaction with iodine (280 mg, 1.1 mmol), t_2=2 h, T_2=20°C, gave after purification by column chromatography (silica, eluent: dichloromethane) 276 mg (80%) of **25** as a white solid, mp 154°C; ^{1}H NMR ($CDCl_3$): δ 4.09 (s, 3H, OCH_3); 4.08 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$): δ 161.1; 158.4; 128.4; 102.9; 56.5; 56.4; IR: ν 2989, 2947, 2858, 1540, 1464, 1443, 1349, 1008, 786, 658 cm^{-1}. MS: $(M)^{+\cdot}$, 344. Anal. Calcd for $C_6H_6BrIN_2O_2$ (344.94): C, 20.89; H, 1.75; N, 8.12. Found: C, 21.08; H, 2.00; N, 8.05.

4-Bromo-3,6-dimethoxypyridazine (26). Exchange reaction of **13** (298 mg, 1.0 mmol) according to the general procedure with *i*-PrMgCl 2.0 M (1 equiv., 0.5 mL), t_1=30 min, T_1=20°C, followed by hydrolysis with water (1 mL), t_2=15 min, T_2=20°C, gave after purification by column chromatography (silica, eluent: dichloromethane) 175 mg (80%) of **26** as a white solid, mp 75°C; ^{1}H NMR ($CDCl_3$): δ 7.21 (s, 1H, H_5); 4.08 (s, 3H, OCH_3); 4.00 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$): δ 162.1; 158.9; 124.2; 119.8; 56.0; 55.4; IR: ν 2955, 1560, 1470, 1367, 1017, 793, 659 cm^{-1}. Anal. Calcd for $C_6H_7N_2O_2Br$ (219.04): C, 32.90; H, 3.22; N, 12.79. Found: C, 32.71; H, 3.46; N, 13.00.

2-Iodo-4-methoxypyrimidine (27). A solution of 2,4-dichloropyrimidine (5.0 g, 33.6 mmol) in aqueous hydroiodic acid (57%, w/w, 30 mL) was vigorously stirred for 8 h at room temperature. The solution was made basic with solid K_2CO_3 (pH=8) and extracted with dichloromethane (5×25 mL). The organic layer was decolorized with sodium thiosulfate, dried over magnesium sulfate and evaporated to give crude 2,4-diiodopyrimidine. Crystallization from petroleum ether afforded 10.0 g (90%) of a white solid, mp 125–126°C; ^{1}H NMR ($CDCl_3$): δ 7.97 (d, J_{6-5}=6.0 Hz, 1H, H_6); 7.80 (d, J_{5-6}=6.0 Hz, 1H, H_5); ^{13}C NMR ($CDCl_3$): δ 157.5; 132.6; 129.7; 127.6; MS: $(M)^{+\cdot}$, 332. A mixture of 2,4-diiodopyrimidine (3.3 g, 10.0 mmol) in methanol (35 mL) containing sodium methylate, which was prepared in situ from sodium metal (230 mg, 10.0 mmol) was refluxed for 5 h. The reaction was monitored by GC. After cooling and hydrolysis with water (10 mL), the methanol was removed under reduced pressure. The aqueous layer was then exctracted three times with dichloromethane (3×15 mL). The organic extract was dried over magnesium sulfate and evaporated to give crude 2-iodo-4-methoxypyrimidine. Purification by column chromatography (silica gel, eluent:dichloromethane) afforded 2.24 g (95%) of **27** as a white solid, mp 133°C; ^{1}H NMR ($CDCl_3$): δ 8.03 (d, J=6.0 Hz, 1H, H_6); 6.63 (d, J=6.0 Hz, 1H, H_5); 3.91 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$): δ 168.8; 158.2; 127.9; 108.3; 55.0; IR: ν 2950, 1585, 1563, 1536, 1461, 1394, 1308, 1218, 1152, 1008, 974, 862, 832, 760, 695 cm^{-1}. MS: $(M)^{+\cdot}$, 236. Anal. Calcd for $C_5H_5IN_2O_2$ (236.01): C, 25.45; H, 2.14; N, 11.87. Found: C, 25.53; H, 2.09; N, 11.98.

2-Hydroxybenzyl-4-methoxypyrimidine (28). Exchange reaction of **27** (236 mg, 1.0 mmol) according to the general procedure with *i*-PrMgCl 2.0 M (1 equiv., 0.5 mL), t_1=1 h, T_1=0°C, followed by reaction with benzaldehyde (0.11 mL, 1.1 mmol), t_2=2 h, T_2=0°C, gave after purification by column chromatography (silica, eluent: dichloromethane) 149 mg (69%) of **28** as a colorless oil, that rapidly decomposed into a brown oil; ^{1}H NMR ($CDCl_3$): δ 8.40 (d, J=5.8 Hz, 1H, H_6); 7.60 (m, 2H, H_{Ph}); 7.30 (m, 3H, H_{Ph}); 6.60 (d, J=5.8 Hz, 1H, H_5); 5.75 (s, 1H, CH); 5.00 (br, 1H, OH); 3.95 (s, 3H, OCH_3).

2-(1-Hydroxy)hexyl-4-methoxypyrimidine (29). Exchange reaction of **27** (236 mg, 1.0 mmol) according to the general procedure with *i*-PrMgCl 2.0 M (1 equiv., 0.5 mL), t_1=1 h, T_1=0°C, followed by reaction with hexanal (0.13 mL, 1.1 mmol), t_2=2 h, T_2=0°C, gave after purification by column chromatography (silica, eluent: dichloromethane)

134 mg (64%) of **29** as a colorless oil; ^{1}H NMR ($CDCl_3$): δ 8.30 (d, J=6.0 Hz, 1H, H_6), 6.53 (d, J=6.0 Hz, 1H, H_5); 4.60 (m, 1H, CH); 4.00 (br, 1H, OH); 3.91 (s, 3H, OCH_3); 1.86 (m, 1H, CH); 1.61 (m, 1H, CH); 1.30 (m, 6H, 3×CH_2); 0.80 (m, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 171.7; 169.9; 156.9; 106.8; 73.5; 54.1; 37.6; 32.1; 25.2; 22.9; 14.0; IR: ν 3456, 2930, 2860, 1582, 1477, 1416, 1333, 1026, 832 cm^{-1}. Anal. Calcd for $C_{11}H_{18}N_2O_2$ (210.28): C, 62.83; H, 8.63; N, 13.32. Found: C, 63.01; H, 8.75; N, 13.20.

Ethyl-4-methoxypyrimidine-2-carboxylate (30). Exchange reaction of **27** (236 mg, 1.0 mmol) according to the general procedure with *i*-PrMgCl 2.0 M (1 equiv., 0.5 mL), t_1=1 h, T_1=0°C, followed by reaction with ethyl cyanoformate (0.11 mL, 1.1 mmol), t_2=12 h, T_2=0°C, gave after purification by column chromatography (silica, eluent: dichloromethane) 109 mg (60%) of **30** as a colorless oil; ^{1}H NMR ($CDCl_3$): δ 8.42 (d, J=5.8 Hz, 1H, H_6); 6.70 (d, J=5.8 Hz, 1H, H_5); 4.15 (q, J=6.8 Hz, 2H, CH_2); 3.97 (s, 3H, OCH_3); 1.27 (t, J=6.8 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 170.5; 158.0; 152.1; 114.1; 109.7; 65.5; 54.8; 14.6; IR: ν 3364, 3105, 2987, 2926, 2855, 1760, 1668, 1588, 1557, 1484, 1418, 1372, 1266, 1151, 1096, 1001, 907, 852, 780 cm^{-1}. Anal. Calcd for $C_8H_{10}N_2O_3$ (182.18): C, 52.74; H, 5.53; N, 15.38. Found: C, 52.70; H, 5.76; N, 15.21.

4-Hydroxybenzyl-2-methylsulfanylpyrimidine (32). Exchange reaction of **31** (252 mg, 1.0 mmol) according to the general procedure with *i*-PrMgCl 2.0 M (1 equiv., 0.5 mL), t_1=30 min, T_1=0°C, followed by reaction with benzaldehyde (0.11 mL, 1.1 mmol), t_2=2 h, T_2=0°C, gave after purification by column chromatography (silica, eluent: dichloromethane) 133 mg (57%) of **32** as a brown solid, mp 88°C; ^{1}H NMR ($CDCl_3$): δ 8.29 (d, J=5.2 Hz, 1H, H_6); 7.25 (m, 5H, H_{Ph}); 6.77 (d, J=5.2 Hz, 1H, H_5); 5.55 (s, 1H, CH); 4.69 (s, 1H, OH); 2.50 (s, 3H, SCH_3); ^{13}C NMR ($CDCl_3$): δ 172.4; 170.3; 157.7; 141.7; 129.1; 128.7; 127.4; 113.6; 75.1; 14.6; IR: ν 3350, 2929, 2871, 1567, 1545, 1351, 1200, 1064, 702, 603 cm^{-1}. MS: $(M)^{+\cdot}$, 232. Anal. Calcd for $C_{12}H_{12}N_2OS$ (232.31): C, 62.04; H, 5.21; N, 12.06. Found: C, 62.25; H, 5.43; N, 11.87.

4-(1-Hydroxy)hexyl-2-methylsulfanylpyrimidine (33). Exchange reaction of **31** (252 mg, 1.0 mmol) according to the general procedure with *i*-PrMgCl 2.0 M (1 equiv., 0.5 mL), t_1=30 min, T_1=0°C, followed by reaction with hexanal (0.13 mL, 1.1 mmol), t_2=2 h, T_2=0°C, gave after purification by column chromatography (silica, eluent: dichloromethane) 124 mg (55%) of **33** as a colorless oil; ^{1}H NMR ($CDCl_3$): δ 8.38 (d, J=5.3 Hz, 1H, H_6); 6.90 (d, J=5.3 Hz, 1H, H_5); 4.55 (m, 1H, CH); 3.60 (br, 1H, OH); 2.49 (s, 3H, SCH_3); 1.70 (m, 2H, CH_2); 1.30 (m, 6H, 3×CH_2); 0.80 (m, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 172.4; 171.9; 159.2; 113.0; 72.8; 38.1; 32.0; 25.6; 23.3; 22.9; 14.4; IR: ν 3391, 2929, 2860, 1567, 1351, 1204, 1074, 837 cm^{-1}. Anal. Calcd for $C_{11}H_{18}N_2OS$ (226.34): C, 58.37; H, 8.02; N, 12.38. Found: C, 58.50; H, 7.88; N, 12.25.

Ethyl-2-methylsulfanylpyrimidine-4-carboxylate (34). Exchange reaction of **31** (252 mg, 1.0 mmol) according to the general procedure with *i*-PrMgCl 2.0 M (1 equiv., 0.5 mL), t_1=30 min, T_1=0°C, followed by reaction with ethyl cyanoformate (0.11 mL, 1.1 mmol), t_2=12 h, T_2=0°C, gave after purification by column chromatography (silica, eluent: dichloromethane) 69 mg (35%) of **34** as a yellow solid, mp 136°C; ^{1}H NMR ($CDCl_3$): δ 8.72 (d, J=5.0 Hz, 1H, H_6); 7.59 (d, J=5.0 Hz, 1H, H_5); 4.40 (q, J=6.8 Hz, 2H, CH_2); 2.63 (s, 3H, SCH_3); 1.38 (t, J=6.8 Hz, 3H, CH_3); IR: ν 3352, 2987, 2944, 1760, 1588, 1557, 1486, 1417, 1371, 1338, 1267, 1150,1097, 1010, 907, 853, 782 cm^{-1}. Anal. Calcd for $C_8H_{10}N_2O_2S$ (198.25): C, 48.47; H, 5.08; N, 14.13. Found: C, 48.35; H, 5.16; N, 13.96.

2-Methylsulfanyl-4-formylpyrimidine (35). Exchange reaction of **31** (252 mg, 1.0 mmol) according to the general procedure with *i*-PrMgCl 2.0 M (1 equiv., 0.5 mL), t_1=30 min, T_1=0°C, followed by reaction with DMF (0.09 mL, 1.1 mmol), t_2=2 h, T_2=0°C, gave after purification by column chromatography (silica, eluent: dichloromethane) 53 mg (34%) of **35** as a white solid, mp 68°C; ^{1}H-NMR ($CDCl_3$): δ 9.87 (s, 1H, CHO); 8.70 (d, J=4.8 Hz, 1H, H_6); 7.36 (d, J=4.8 Hz, 1H, H_5); 2.56 (s, 3H, SCH_3); ^{13}C NMR ($CDCl_3$): δ 193.0; 174.8; 159.6; 158.1; 111.9; 14.6; IR: ν 3402, 3124, 3064, 2929, 2849, 1736, 1711, 1554, 1467, 1426, 1366, 1323, 1256, 1214, 1180, 1078, 971, 877, 854, 768, 748, 720, 652, 477 cm^{-1}. Anal. Calcd for $C_6H_6N_2OS$ (154.19): C, 46.74; H, 3.92; N, 18.17. Found: C, 46.68; H, 3.76; N, 18.30.

2-Hydroxybenzylpyrazine (40). Exchange reaction of **36** (206 mg, 1.0 mmol) according to the general procedure with *n*-BuMgCl 2.0 M (1 equiv., 0.5 mL), t_1=30 min, T_1=0°C, followed by reaction with benzaldehyde (0.11 mL, 1.1 mmol), t_2=2 h, T_2=0°C, gave after purification by column chromatography (silica, eluent: dichloromethane) 109 mg (59%) of **40** as an orange solid, mp 108°C; ^{1}H NMR ($CDCl_3$): δ 8.49 (s, 1H, H_3); 8.28 (m, 2H, $H_{5,6}$); 7.23 (m, 5H, H_{Ph}); 5.74 (s, 1H, CH); 5.02 (br, 1H, OH); IR: ν 3320, 3060, 1493, 1453, 1402, 1148, 1062, 1018, 701 cm^{-1}. Anal. Calcd for $C_{11}H_{10}N_2O$ (186.22): C, 70.95; H, 5.41; N, 15.04. Found: C, 70.72; H, 5.59; N, 14.98.

(1-Hydroxy)hexylpyrazine (41). Exchange reaction of **36** (206 mg, 1.0 mmol) according to the general procedure with *n*-BuMgCl 2.0 M (1 equiv., 0.5 mL), t_1=30 min, T_1=0°C, followed by reaction with hexanal (0.13 mL, 1.1 mmol), t_2=2 h, T_2=0°C, gave after purification by column chromatography (silica, eluent: dichloromethane) 60 mg (33%) of **41** as a colorless oil; ^{1}H NMR ($CDCl_3$): δ 8.57 (s, 1H, H_3); 8.42 (m, 2H, $H_{5,6}$); 4.74 (m, 1H, CH); 3.73 (br, 1H, OH); 1.75 (m, 2H, CH_2); 1.24 (m, 6H, 3×CH_2); 0.79 (m, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 158.6; 143.7; 143.6; 143.2; 72.3; 38.6; 32.0; 25.3; 22.9; 14.4; IR: ν 3369, 2956, 2930, 2859, 1694, 1529, 1469, 1403, 1312, 1152, 1121, 1058, 1018, 928, 845, 768, 727, 680 cm^{-1}. Anal. Calcd for $C_{10}H_{16}N_2O$ (180.25): C, 66.64; H, 8.95; N, 15.54. Found: C, 66.58; H, 9.17; N, 15.38.

2-Hydroxybenzyl-3-methoxypyrazine (42). Exchange reaction of **37** (236 mg, 1.0 mmol) according to the general procedure with *i*-PrMgCl 2.0 M (1 equiv., 0.5 mL), t_1=30 min, T_1=0°C, followed by reaction with benzaldehyde (0.11 mL, 1.1 mmol), t_2=2 h, T_2=0°C, gave after purification by column chromatography (silica, eluent: dichloromethane) 121 mg (56%) of **42** as a white solid,

mp 98°C; ^{1}H NMR ($CDCl_3$): δ 8.03 (d, J=0.1 Hz, 1H, H_5); 7.95 (d, J=0.1 Hz, 1H, H_6); 7.25 (m, 5H, H_{Ph}); 5.80 (d, J=6.0 Hz, 1H, CH); 4.85 (d, J=6.0 Hz, 1H, OH); 3.84 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$): δ 157.6; 146.7; 142.0; 140.3; 135.0; 128.7; 128.1; 127.4; 71.2; 54.1; IR: ν 3459, 3059, 2953, 2859, 1546, 1462, 1385, 1312, 1185, 1116, 1071, 1011, 843 cm^{-1}. Anal. Calcd for $C_{12}H_{12}N_2O_2$ (216.24): C, 66.65; H, 5.59; N, 12.95. Found: C, 66.40; H, 5.80; N, 12.62.

2-(1-Hydroxy)hexyl-3-methoxypyrazine (43). Exchange reaction of **37** (236 mg, 1.0 mmol) according to the general procedure with *i*-PrMgCl 2.0 M (1 equiv., 0.5 mL), t_1=30 min, T_1=0°C, followed by reaction with hexanal (0.13 mL, 1.1 mmol), t_2=2 h, T_2=0°C, gave after purification by column chromatography (silica, eluent: dichloromethane) 105 mg (50%) of **43** as a colorless oil; ^{1}H NMR ($CDCl_3$): δ 7.97 (d, J=5.9 Hz, 1H, H_5); 7.95 (d, J=5.9 Hz, 1H, H_6); 4.82 (m, 1H, CH); 3.92 (s, 3H, OCH_3); 3.60 (br, 1H, OH); 2.25 (m, 1H, CH); 1.75 (m, 1H, CH); 1.30 (m, 6H, 3×CH_2); 0.79 (m, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 157.6; 148.2; 139.7; 135.0; 69.3; 54.0; 36.6; 31.8; 25.6; 23.0; 14.3; IR: ν 3454, 2930, 2860, 1731, 1546, 1461, 1384, 1313, 1268, 1172, 1116, 1070, 1034, 1012, 843 cm^{-1}. Anal. Calcd for $C_{11}H_{18}N_2O_2$ (210.28): C, 62.83; H, 8.63; N, 13.32. Found: C, 62.76; H, 8.50; N, 13.50.

2-Formyl-3-methoxypyrazine (44). Exchange reaction of **37** (236 mg, 1.0 mmol) according to the general procedure with *i*-PrMgCl 2.0 M (1 equiv., 0.5 mL), t_1=30 min, T_1=0°C, followed by reaction with DMF (0.09 mL, 1.1 mmol), t_2=2 h, T_2=0°C, gave after purification by column chromatography (silica, eluent: dichloromethane) 138 mg (51%) of **44** as a white solid, mp 66–67°C; ^{1}H NMR ($CDCl_3$): δ 10.25 (s, 1H, CHO); 8.35 (s, 2H, $H_{5,6}$); 4.10 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$): δ 190.3, 160.8, 146.0, 137.7, 136.4, 54.8; ir: ν 3408, 3067, 3010, 2956, 2798, 2707, 1711, 1569, 1534, 1471, 1443, 1398, 1366, 1306, 1224, 1153, 1074, 996, 894, 876, 766, 665, 602 cm^{-1}. Anal. Calcd for $C_6H_6N_2O_2$ (138.13): C, 52.17; H, 4.38; N, 20.28. Found: C, 52.39; H, 4.59; N, 20.00.

2-Hydroxybenzyl-3-chloropyrazine (45). Exchange reaction of **38** (240.5 mg, 1.0 mmol) according to the general procedure with *n*-Bu_2Mg 2.0 M (1 equiv., 0.5 mL), t_1=30 min, T_1=0°C, followed by addition of triethylamine (0.14 mL, 1.0 mmol). After 10 min under stirring, the reaction with benzaldehyde (0.11 mL, 1.1 mmol), t_2=2 h, T_2=0°C, gave after purification by column chromatography (silica, eluent: dichloromethane) 97 mg (44%) of **45** as an orange oil; ^{1}H NMR ($CDCl_3$): δ 8.45 (d, J=2.5 Hz, 1H, H_5); 8.26 (d, J=2.5 Hz, 1H, H_6); 7.24 (m, 5H, H_{Ph}); 5.95 (d, J=7.0 Hz, 1H, CH); 4.60 (d, J=7.0 Hz, 1H, OH); ^{13}C NMR ($CDCl_3$): δ 155.2; 148.0; 143.5; 141.6; 140.7; 129.0; 128.7; 127.9; 72.5; IR: ν 3370, 2900, 1600, 1375, 1050 cm^{-1}. Anal. Calcd for $C_{11}H_9ClN_2O$ (220.66): C, 59.88; H, 4.11; N, 12.70. Found: C, 60.09; H, 4.38; N, 12.95.

2-(1-Hydroxy)hexyl-3-chloropyrazine (46). Exchange reaction of **38** (240.5 mg, 1.0 mmol) according to the general procedure with *n*-BuMgCl 2.0 M (1 equiv., 0.5 mL), t_1=30 min, T_1=0°C, followed by reaction with hexanal (0.13 mL, 1.1 mmol), t_2=2 h, T_2=0°C, gave after purification by column chromatography (silica, eluent: dichloromethane) 42 mg (20%) of **46** as a colorless oil; ^{1}H NMR ($CDCl_3$): δ 8.61 (d, J=2.6 Hz, 1H, H_5); 8.48 (d, J=2.6 Hz, 1H, H_6); 4.15 (m, 1H, CH); 3.50 (br, 1H, OH); 2.25 (m, 2H, CH_2); 1.18 (m, 6H, 3×CH_2); 0.83 (m, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 154.9; 141.4; 140.5; 124.2; 70.0; 36.8; 31.7; 24.9; 22.4; 13.9; IR: ν 3450, 2956, 2926, 2855, 1729, 1465, 1378, 1347, 1288, 1142, 1091, 1058, 1024, 859, 737 cm^{-1}. Anal. Calcd for $C_{10}H_{15}ClN_2O$ (214.70): C, 55.94; H, 7.04; N, 13.05. Found: C, 55.98; H, 6.86; N, 13.15.

3-Hydroxybenzyl-2-iodopyrazine (47). Exchange reaction of **39** (332 mg, 1.0 mmol) according to the general procedure with *n*-BuMgCl 2.0 M (1 equiv., 0.5 mL), t_1=30 min, T_1=0°C, followed by reaction with benzaldehyde (0.11 mL, 1.1 mmol), t_2=2 h, T_2=0°C, gave after purification by column chromatography (silica, eluent: dichloromethane) 33 mg (11%) of **47** as a yellow oil; ^{1}H NMR ($CDCl_3$): δ 8.46 (d, 1H, J=2.5 Hz, H_5); 8.24 (d, 1H, J=2.5 Hz, H_6); 7.27 (m, 5H, H_{Ph}); 5.94 (d, 1H, J=7.8 Hz, CH); 4.72 (br, 1H, OH); IR: ν 3401, 2926, 2856, 1727, 1513, 1494, 1455, 1362, 1188, 1136, 1081, 1024, 862, 757, 699 cm^{-1}. Anal. Calcd for $C_{11}H_9N_2OI$ (312.11): C, 42.33; H, 2.91; N, 8.98. Found: C, 42.50; H, 3.22; N, 8.76.

References

1. Turck, A.; Plé, N.; Leprêtre-Gaquère, A.; Quéguiner, G. *Heterocycles* **1998**, *49*, 205.
2. Langley, B. W. *J. Am. Chem. Soc.* **1956**, *78*, 2136.
3. Shimura, A.; Momotake, A.; Togo, H.; Yokoama, M. *Synthesis*, **1999**, *3*, 495; Momotake, A.; Mito, J.; Yamaguchi, K.; Togo, H.; Yokoyama, M. *J. Org. Chem.*, **1998**, *63*, 7207; Momotake, A.; Togo, H.; Yokoyama, M. *J. Chem. Soc., Perkin Trans. 1*, **1999**, 1193.
4. Bérillon, L.; Leprêtre, A.; Turck, A.; Plé, N.; Quéguiner, G.; Cahiez, G.; Knochel, P. *Synlett* **1998**, 1359–1360.
5. Röttlander, M.; Boymond, L.; Bérillon, L.; Leprêtre, A.; Varchi, G.; Avolio, S.; Laaziri, H.; Quéguiner, G.; Ricci, A.; Cahiez, G.; Knochel, P. *Chem. Eur. J.* **1999**, in press.
6. Trécourt, F.; Breton, G.; Bonnet, V.; Mongin, F.; Marsais, F.; Quéguiner, G. *Tetrahedron Lett.* **1999**, *40*, 4339–4342.
7. Ndzi, B. Thesis, University of Rouen, France, 1990.
8. Breton, G. Thesis, University of Rouen, France, 1999.
9. Plé, N.; Turck, A.; Heynderickx, A.; Quéguiner, G. *Tetrahedron* **1998**, *54*, 9701–9710.
10. Trohay, D. Thesis, University of Rouen, France, 1990.
11. Mojovic, L. Thesis, University of Rouen, France, 1990.