A New Route to Aminodiazines via Metalation Reaction. Synthesis of an Aza Analogue of Nevirapine: Diazines XV

Nelly Plé, Alain Turck, Karine Couture, Guy Quéguiner*

Laboratoire de Chimie Organique Fine de l'IRCOF associé au CNRS, INSA de Rouen, BP 08, F-76131 Mont-Saint-Aignan cédex, France

Fax +33(35)528484; E-mail guyqueguiner@Insa-rouen-fr

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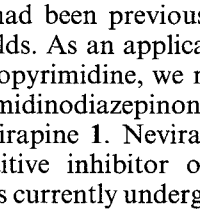
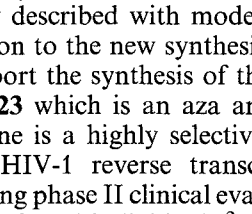
A new route to aminodiazines is reported, the *ortho*-directed lithiation of diazines is used, followed by reaction with tosyl azide as an electrophile. The reduction of the azido or tetrazolo compounds obtained was achieved and led to the expected amines. This methodology has allowed the synthesis of new aminodiazines and an improvement in the yield of various aminodiazines previously described. This reaction was used for the preparation of an aza analogue of Nevirapine.

Several antibacterial sulfonamides such as Sulfadiazine, Madribon, Sulfamethoxypyridazine, CS 61, and Kelfizine are usually manufactured by reaction of acetamidobenzenesulfonyl chloride with the amino derivative of a diazine.[1,2] The aminomethoxydiazines are generally the precursors of these sulfonamides. We report here a new synthetic route to aminomethoxydiazines for which the synthesis had been previously described with moderate or low yields. As an application to the new synthesis of an 5-aminopyrimidine, we report the synthesis of the pyridopyrimidinodiazepinone **23** which is an aza analogue of Nevirapine **1**. Nevirapine is a highly selective, noncompetitive inhibitor of HIV-1 reverse transcriptase which is currently undergoing phase II clinical evaluation for the treatment of HIV-infected individuals.[3]



1 (Nevirapine)



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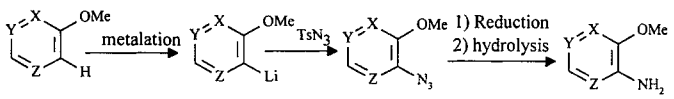
Methods of making aminodiazines fall into three main categories: 1) the formation of diazine by condensation with appropriate compounds (major method), 2) the nucleophilic displacement of a leaving group by ammonia or amines (however, products must be stable under the conditions of the reaction), and 3) the reduction, degradation or modification of other groups in this manner. The reduction of azido or tetrazolo groups may be used to synthesize primary amines. The azido derivatives could be obtained either by nitrosation of hydrazines[4] or nucleophilic displacement of halogen.[5-7] More recently, another method has been described involving the reaction of tosyl azide with a lithio derivative.[8-10]

We report here the synthesis of various aminodiazines using this last methodology which had never been applied to diazines and which allows an improvement, with fewer steps, in the synthesis of some aminodiazines previously described with moderate or low yields.

The general principle of this new synthetic route to aminomethoxydiazines via metalation is summarized (Scheme 1). Treatment of a methoxydiazine with a twofold excess of metalating agent in THF at −75 °C followed by reaction with tosyl azide led to the expected azido derivative. However, when the azido group was *ortho* to a ring nitrogen atom, a fast cyclization occured leading to a tetrazolo derivative.[4] Nevertheless, the reduction of the azido or tetrazolo derivative led to the expected aminodiazine (Scheme 1).



X	Y	Z
N	CH	N
CH	N	N
N	N	CH

Scheme 1

The reduction of the azido group was generally successfully achieved either by hydrogen sulfide[11,12] or by catalytic reduction using 10% Pd/C and hydrogen.[13,14] The reduction of the tetrazolo group could be performed by reaction with triphenylphosphane leading to a phosphazene derivative which gave the expected amine upon hydrolysis.[15]

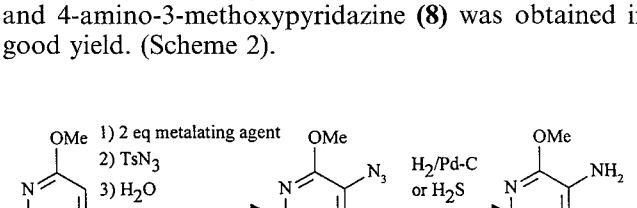
The metalation of 3,6-disubstituted pyridazines followed by reaction with tosyl azide led to azido compounds which were reduced to the expected aminopyridazines. According to this procedure, 3,6-dimethoxypyridazine **(2)** led to the 4-aminoderivative **6** which was the precursor of the sulfonamide CS 61.[16]

The metalation of **2** was performed either with lithium 2,2,6,6-tetramethylpiperidide (LTMP) or BuLi as metalating agent. The exceptional use of BuLi as metalating agent in this case may be noted. We had previously reported[17] that the π-deficient character of diazines allows, with good nucleophiles such as alkyllithium, easy competitive nucleophilic addition which occurs on neighbouring carbons of the cyclic nitrogens. With 3,6-dimethoxypyridazine, the presence of substituents on these carbons partially inhibits this nucleophilic attack and allows the use of BuLi as metalating agent if short reaction times are used. A better yield was obtained using 1 equivalent of BuLi at −75 °C with a short reaction time (10 min) followed by reaction of tosyl azide to give the azido

compound **4** in 73% yield. A catalytic reduction of **4** with palladium on charcoal gave quantitatively the amine **6** which was obtained in an overall yield of 73% starting from **2** (Scheme 2). The synthesis of **6** has been previously described from **2** by Van Der Plas with an overall yield of 50%.[18]

When the metalation of the unsymmetrical disubstituted pyridazine **3** was performed with LTMP or LDA as metalating agent, followed by reaction with various electrophiles, the reaction was not regioselective and a mixture of 4- and 5-substituted compounds was obtained.[19]

When LTMP, a bulkier base than LDA, was used as metalating agent, the metalation was more regioselective *ortho* to the methoxy group. This result led us to investigate the use of a more hindered base than LTMP such as lithium *tert*-butyl-(1-isopropylpentyl)amide[20] to enhance regioselective metalation at C4. Under these conditions, the azido compound **5** was obtained quantitatively. The reduction of the azido group with hydrogen sulfide in the presence of piperidine gave the amine **7** in moderate yield. However, using catalytic reduction with 10% Pd/C and hydrogen, the chlorine atom was removed and 4-amino-3-methoxypyridazine **(8)** was obtained in good yield. (Scheme 2).

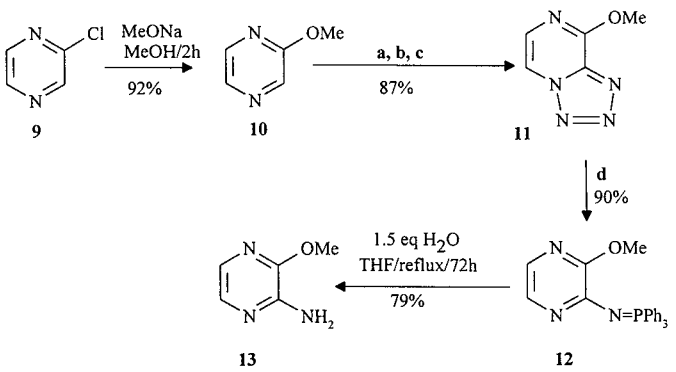


Scheme 2

This new synthetic route offers an improvement in the synthesis of **8** which had been previously described by Yanai[16] in 28% yield starting from 3,4,6-trichloropyridazine. 2-Amino-3-methoxypyrazine **(13)** is the precursor of the sulfonamide Kelfizine or Sulfalene known for its antibacterial activity.[1] The synthesis of the amine **13** had been performed by building of the pyrazine ring by condensation[21] or from 2-aminopyrazine-3-carboxylic acid[22] in moderate yield (20–30%).

Our synthetic route starts from 2-methoxypyrazine **(10)**, easily obtained from 2-chloropyrazine **(9)**. Treatment of **10** with 2.1 equivalents of LTMP at −75 °C followed by reaction with tosyl azide led to the tetrazolo compound **11** which underwent reaction with triphenylphosphane in benzene to give the intermediate phosphazene **12**. Hydrolysis of **12** afforded the expected **13** in four steps from **9** with an overall yield of 57%. (Scheme 3).

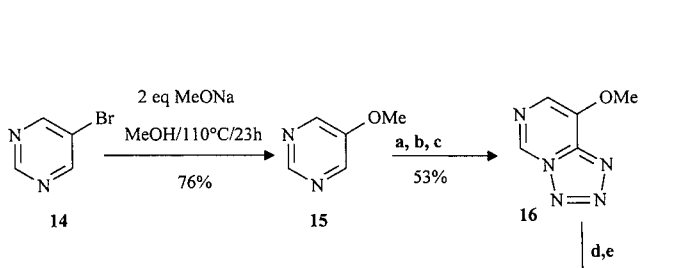
A similar route applied to 5-methoxypyrimidine **(15)**, easily obtained by reaction of the commercially available 5-bromopyrimidine **(14)** with sodium methoxide, allowed us to obtain 4-amino-5-methoxypyrimidine **(17)** in four steps with an overall yield of 32% (Scheme 4). The amino-



(a) 2.1 equiv LTMP/THF/−75 °C/1.5 h, (b) TsN_3/−75 °C/2 h, (c) H_2O, (d) PPh_3, benzene, reflux 65 h

Scheme 3

pyrimidine **17** was used as a precursor in the synthesis of pyrimido[1,2-*a*]pyrimidin-4-one, an isostere of the antibacterial pyridopyrimidin-4-one[23] and its synthesis had been previously reported by Chesterfield[24] in five steps from methyl methoxyacetate in 7.7% overall yield.

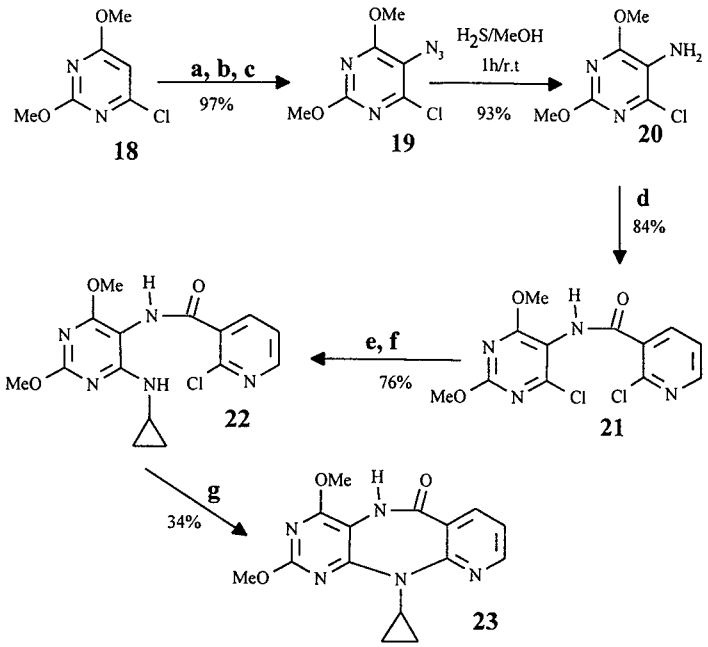


(a) 2.1 equiv LTMP/THF/−75 °C/1 h,
(b) 2.3 equiv TsN_3/−75 °C/2 h, (c) H_2O,
(d) PPh_3, benzene, reflux 65 h, (e) HOAc, 80%, reflux 20 min

Scheme 4

As an application of the new route to aminodiazines, we report here the synthesis of an aza analogue **23** of Nevirapine **1** (Scheme 5).

Metalation of 6-chloro-2,4-dimethoxypyrimidine **(18)** using BuLi in THF at −75 °C under short reaction times (10 min) followed by reaction with tosyl azide led to the azido compound **19** in good yield. The reduction by hydrogen sulfide gave the expected amino derivative **20** in high yield. The condensation of the amine **20** with 2-chloronicotinoyl chloride afforded the amide **21**. Since compound **21** has two chlorine atoms which are both very prone to nucleophilic displacement, some problems were encountered in the regioselective displacement of only one chlorine atom. The best results were obtained by heating 1 equivalent of cyclopropylamine in the presence of triethylamine in butanol at 60 °C under pressure. Under these conditions, only the chlorine atom of the pyrimidine nucleus underwent displacement and no ring-



(a) 1.1 equiv BuLi/THF/ − 75 °C/10 min,
(b) 1.5 equiv TsN_3/75 °C, 2 h, (c) H_2O,
(d) 1.3 equiv 2-chloronicotinoyl chloride, CH_2Cl_2, r.t., 3 h,
(e) 1 equiv cyclopropylamine,
(f) 1.2 equiv Et_3N/BuOH/60 °C/120 h
(g) 4 equiv NaH, diglyme, 140 °C, 1 h

Scheme 5

closed product was observed. When the cyclization of amide **22** was carried out by heating with sodium hydride in diglyme at 140 °C for 1 hour, the aza analogue **23** of Niverapine was obtained. Thus, starting from the commercially available **18**, we have obtained the aza analogue **23** of Nevirapine in 5 steps with an overall yield of 20 % (Scheme 5).

Melting points were measured on a Koffler apparatus. ^1H NMR spectra were recorded (in ppm) on a 200 MHz Bruker spectrometer (internal standard: TMS in $CDCl_3$ or HMDS in DMSO-d_6). IR spectra were taken on a Beckman IR 4250 spectrometer, and main absorption frequencies (NH, CH, C=O, C=C, C=N) are given in cm^{-1}. Mass spectra were obtained on a JEOL D700 instrument (chemical ionization in NH_3), and elemental analyses were performed on a Carlo Erba CHN apparatus. Satisfactory microanalyses were obtained for all new compounds: C ± 0.42, H ± 0.34, N ± 0.36. THF was distilled from benzophenone/Na. The water content of the solvent was estimated lower than 45 ppm by the modified Karl-Fischer method[25]. All reagents and 3,6-dichloropyridazine, 2-chloropyrazine and 5-bromopyrimidine were of commercial quality and were purchased from Aldrich Chemical Co or Acros organics. 3,6-dimethoxypyridazine **(2)** and 2-chloro-6-methoxypyridazine **(3)** were prepared from 3,6-dichloropyridazine according to a classical procedure,[26] and 2-methoxypyrazine **(10)** from 2-chloropyrazine.[27]

Commercial 2.5 M solution of BuLi in hexane was stored and transferred under anhyd and deoxygenated Ar. Lithium 2,2,6,6-tetramethylpiperidide (LTMP) or lithium *tert*-butyl-2-(isopropylpentyl) amide were prepared by reaction of the appropriate amine (3.03 mmol) in THF (20 mL) and BuLi (1.29 mL, 2.5 M, 3.03 mmol) at − 30 °C and then at 0 °C for 30 min.

4-Azido-3,6-dimethoxypyridazine (4):
BuLi (0.68 mL, 1.59 mmol) was slowly added to a cold solution (− 75 °C) of 3,6-dimethoxypyridazine (**2**; 0.202 g, 1.44 mmol) in anhyd THF (36 mL). The resulting solution was stirred for 10 min at − 75 °C before addition of TsN_3 (0.314 g, 1.59 mmol) in THF (10 mL). The solution was stirred for 2 h at − 75 °C, then warmed slowly to r.t. Then sat $NaHCO_3$ was added (to pH = 7.5). Extraction with CH_2Cl_2 (2 × 20 mL), drying ($MgSO_4$) and removal of solvent afforded a crude solid which was purified by flash chromatography on silica gel (20 g; eluent: CH_2Cl_2/EtOAc, 4 : 1); yield: 0.19 g (73 %); mp dec 35 °C.

^1H NMR ($CDCl_3$): δ = 4.02 (s, 3 H, OCH_3), 4.11 (s, 3 H, OCH_3), 6.49 (s, 1 H, H_5).

IR (KBr): ν = 2956, 2126, 1605, 1473, 1392 cm^{-1}.

$C_6H_7N_5O_2$ (181.18):	calc.	C 39.77	H 3.90	N 38.66
	found	40.03	3.86	38.35

4-Azido-6-chloro-3-methoxypyridazine (5):
6-Chloro-3-methoxypyridazine (**3**; 0.29 g, 2 mmol) in THF (10 mL), was slowly added to a cold (− 75 °C) solution of lithium *tert*-butyl-2-(isopropylpentyl) amide (4.2 mmol) in THF (30 mL). The resulting mixture was stirred for 30 min at − 75 °C before the addition of TsN_3 (0.827 g, 4.2 mmol) in THF (10 mL). Stirring was continued for 2 h at the same temperature before hydrolysis by a mixture of 35 % HCl, EtOH, THF (1 mL, 2 mL, 2 mL), then the temperature was slowly increased to r.t., and sat $NaHCO_3$ was added (to pH = 8). Extraction with CH_2Cl_2 (2 × 20 mL), drying ($MgSO_4$) and removal of solvent afforded a crude product which was purified by flash chromatography on silica gel (20 g; eluent: CH_2Cl_2/EtOAc, 1 : 1); yield: 0.37 g (100 %); mp dec 35 °C.

^1H NMR ($CDCl_3$): δ = 4.17 (s, 3 H, OCH_3), 6.95 (s, 1 H, H_5).

IR (KBr): ν = 2982, 2125, 2092, 1608, 1477 cm^{-1}.

$C_5H_4ClN_5O$ (185.59):	calc.	C 32.36	H 2.18	N 37.74
	found	32.46	2.37	37.56

4-Amino-3,6-dimethoxypyridazine (6):
A solution of **4** (1.0 g, 5.52 mmol) in EtOH (100 mL) containing 0.2 g of 10 % Pd/C catalyst was hydrogenated at atmospheric pressure. Uptake of H_2 was complete in 2 h. The catalyst was removed by filtration through Celite and the filtrate evaporated to dryness under reduced pressure to give **6** in analytical purity; yield: 0.86 g (100 %); mp 180 °C, Lit.[18] mp 178–180 °C.

^1H NMR (DMSO-d_6): δ = 3.65 (s, 3 H, OCH_3), 3.77 (s, 3 H, OCH_3), 3.8–3.6 (m, 2 H, NH_2), 5.37 (s, 1 H, H_5).

IR (KBr): ν = 3300, 3000, 1739, 1654, 1560, 1542, 1400 cm^{-1}.

$C_6H_9N_3O_2$ (155.18):	calc.	C 46.44	H 5.86	N 27.08
	found	46.80	5.52	27.35

4-Amino-6-chloro-3-methoxypyridazine (7):
A solution of **5** (0.75 g, 4.0 mmol) and piperidine (0.25 mL, 2.5 mmol) in MeOH (10 mL) was cooled to 10 °C. H_2S was bubbled through the solution for 30 min, and the temperature was maintained between 10 °C and 20 °C. After filtration of the sulfur and removal of the solvent, the crude product was purified by flash chromatography on silica gel (35 g; eluent CH_2Cl_2/EtOAc, 8 : 2); yield: 0.25 g (40 %); mp 206 °C.

^1H NMR ($CDCl_3$): δ = 3.96 (s, 3 H, OCH_3), 6.63 (m, 2 H, NH_2), 6.54 (s, 1 H, H_5).

IR (KBr): ν = 3465, 3283, 3053, 1640, 1573 cm^{-1}.

$C_5H_6ClN_3O$ (155.59):	calc.	C 37.63	H 3.78	N 26.34
	found	37.19	3.66	26.03

4-Amino-3-methoxypyridazine (8):
A solution of **5** (1.0 g, 5.38 mmol) in EtOH (100 mL) containing 0.2 g of 10 % Pd/C catalyst was hydrogenated at atmospheric pressure. Uptake of H_2 was complete in 2 h. The catalyst was removed by filtration through Celite and the filtrate evaporated to dryness under reduced pressure. The product **8** was obtained in analytical purity. Yield: 0.57 g (84 %); mp 126 °C, Lit.[16] mp 127–128 °C.

^1H NMR ($CDCl_3$): δ = 4.00 (s, 3 H, OCH_3), 7.00 (d, 1 H, H_5), 8.49 (m, 2 H, NH_2), 8.55 (d, 1 H, H_6), $J_{5,6}$ = 6.5 Hz.

IR (KBr): ν = 3330, 3118, 1646, 1577, 1521 cm^{-1}.

MS (EI): m/z = 125 (M).

$C_5H_7N_3O$ (125.15): calc. C 47.98 H 5.64 N 33.58
found 48.34 5.41 33.32

2-Methoxypyrazine (10):
To a stirred solution of MeONa (1.9 g, 35 mmol) in MeOH (30 mL) was added 2-chloropyrazine (2.0 g, 17.5 mmol). The mixture was refluxed for 2 h. After cooling to r.t. H_2O (20 mL) was added, then the mixture was concentrated in vacuo to a volume of about 20 mL and extracted with Et_2O (2 × 20 mL), dried ($MgSO_4$) and solvent removal afforded a liquid which was purified by distillation (37 °C, 28 mbar); yield: 1.77 g (92%).

^{1}H NMR ($CDCl_3$): δ = 3.87 (s, 3 H, OCH_3), 8.00 (s, 2 H, H_3, H_5), 8.12 (s, 1 H, H_6).

IR (KBr): ν = 3061, 2986, 2857, 1581, 1474, 1397 cm^{-1}.

$C_5H_6N_2O$ (110.13): calc. C 54.53 H 5.50 N 25.44
found 54.22 5.55 25.33

8-Methoxytetrazolo[1,5-*a*]pyrazine (11):
2-Methoxypyrazine (**10**, 0.2 g, 1.82 mmol) in THF (10 mL) was slowly added to a cold (− 75 °C) solution of LTMP (3.82 mmol) in THF (30 mL). The resulting mixture was stirred for 1 h at − 75 °C before the addition of TsN_3 (0.75 g, 3.8 mmol) in THF (10 mL). Stirring was continued for 2 h at the same temperature before hydrolysis by a mixture of 35% aq HCl/EtOH/THF (1 mL, 2 mL, 2 mL). Then the temperature was slowly increased to r.t. and sat $NaHCO_3$ was added (to pH = 8). Extraction with CH_2Cl_2 (2 × 20 mL), drying ($MgSO_4$) and removal of solvent afforded a crude product which was purified by flash chromatography on silica gel (20 g; eluent: CH_2Cl_2); yield: 0.61 g (87%); mp 140 °C.

^{1}H NMR ($CDCl_3$): δ = 4.20 (s, 3 H, OCH_3), 7.70 (d, 1 H, H_6), 8.83 (d, 1 H, H_5), $J_{5,6}$ = 5 Hz.

IR (KBr): ν = 3118, 3015, 2946, 1543, 1490, 1358 cm^{-1}.

$C_{23}H_{20}N_3O$ (385.46): calc. C 71.66 H 5.24 N 10.90
found 71.96 5.22 10.62

***N*-(2-Methoxy-3-pyrazinyl)triphenylphosphazene (12):**
A mixture of **11** (0.5 g, 3.3 mmol) and PPh_3 (0.95 g, 3.6 mmol) in benzene (10 mL) was refluxed for 65 h. Cooling and removal of the solvent afforded a crude product which was washed by cyclohexane (3 × 10 mL) and no further purification was necessary. Yield: 0.44 g (90%); mp 199 °C.

^{1}H NMR ($CDCl_3$): δ = 3.97 (s, 3 H, OCH_3), 8.00 to 7.30 (m, 17 H, Ph, H_5, H_6).

IR (KBr): ν = 3046, 1570, 1458, 1436, 1414, 1300 cm^{-1}.

$C_5H_5N_5O$ (151.15): calc. C 39.73 H 3.34 N 46.36
found 39.47 3.41 45.91

2-Amino-3-methoxypyrazine (13):
A mixture of **12** (0.45 g, 3 mmol), H_2O (0.081 mL) and THF (10 mL) was refluxed for 72 h. Cooling and removal of the solvent afforded an amide product which was dissolved in toluene (20 mL). This was then extracted by a solution of 30% HCl (3 × 30 mL) followed by the addition of sat $NaHCO_3$ (to pH = 8.5). The aqueous solution was extracted by CH_2Cl_2 (3 × 20 mL). Drying ($MgSO_4$) and removal of the solvent afforded the product, in analytical purity. Yield: 0.30 g (79%); mp 83 °C, Lit.[21,22] mp 80–82 °C.

^{1}H NMR ($CDCl_3$): δ = 4.00 (s, 3 H, OCH_3), 4.83 (m, 2 H, NH_2), 7.33 (d, 1 H), 7.47 (d, 1 H), $J_{5,6}$ = 3 Hz.

IR (KBr): ν = 3408, 3171, 2990, 1648, 1546, 1495, 1309 cm^{-1}.

$C_5H_7N_3O$ (125.15): calc. C 47.98 H 5.65 N 33.58
found 47.87 5.88 33.69

5-Methoxypyrimidine (15):
A solution of 5-bromopyrimidine (**14**, 2 g, 12.6 mmol), NaOMe (1.36 g, 25.2 mmol) in MeOH (40 mL) was warmed in a pressure vessel for 24 h at 110 °C (under a pressure of 35 bar). After cooling and hydrolysis with H_2O (50 mL), the mixture was concentrated in vacuo to a volume of about 50 mL and extracted by CH_2Cl_2 (3 × 15 mL), dried ($MgSO_4$) and solvent removal afforded the crude product, which was purified by flash chromatography on silica gel (70 g; eluent: CH_2Cl_2/EtOac, 4 : 1); yield: 1.05 g (76%); mp 43 °C.

^{1}H NMR ($CDCl_3$): δ = 3.87 (s, 3 H, OCH_3), 8.40 (s, 2 H, H_4, H_6), 8.85 (s, 1 H, H_2).

IR (KBr): ν = 2972, 2849, 1565, 1443, 1280 cm^{-1}.

$C_5H_6N_2O$ (110.13): calc. C 54.53 H 5.50 N 25.44
found 54.15 5.51 25.51

8-Methoxytetrazolo[1,5-*c*]pyrimidine (16):
5-Methoxypyrimidine (**15**, 0.2 g, 1.82 mmol) in THF (10 mL) was slowly added to a cold (− 75 °C) solution of LTMP (3.82 mmol) in THF (30 mL). The resulting mixture was stirred 1.5 h at − 75 °C before addition of TsN_3 (0.75 g, 3.8 mmol) in THF (10 mL) and stirring was continued for 2 h at the same temperature before hydrolysis by a mixture of 35% aq HCl/EtOH/THF (1 mL, 2 mL, 2 mL). Then the temperature was slowly increased to r.t. and sat $NaHCO_3$ was added (to pH = 8.5). Extraction with CH_2Cl_2 (3 × 20 mL), drying ($MgSO_4$) and removal of solvent afforded a crude product which was purified by flash chromatography on silica gel (20 g; eluent: CH_2Cl_2); yield: 0.15 g (53%); mp 152 °C.

^{1}H NMR ($CDCl_3$): δ = 3.95 (s, 3 H, OCH_3), 8.18 (s, 1 H, H_6), 8.55 (s, 1 H, H_2).

IR (KBr): ν = 3070, 3060, 1630, 1560, 1490 cm^{-1}.

MS (CI): m/z = 152 (M^+).

4-Amino-5-methoxypyrimidine (17):
A solution of **16** (0.6 g, 3.9 mmol), PPh_3 (1.1 g, 4.1 mmol) in benzene (10 mL) was refluxed for 65 h. After the removal of benzene and addition of cyclohexane (10 mL), the precipitate obtained was filtered and washed with cyclohexane (3 × 10 mL) to remove the triphenylphosphane oxide. The crude product was dissolved in 80% aq HOAc (10 mL), then the solution was refluxed for 20 min, this was followed by cooling, addition of H_2O (5 mL) and extraction with EtOAc (2 × 15 mL). The aqueous layer was evaporated and the crude product was dissolved in 20 mL of Et_2O. Then this was extracted with 30% aq HCl (2 × 20 mL) and the aqueous layers were basified with $NaHCO_3$ (to pH = 8.5). The aqueous solution was extracted with CH_2Cl_2 (2 × 20 mL), dried ($MgSO_4$) and removal of the solvent afforded the product in analytical purity. Yield: 0.30 g (60%); mp 118 °C, Lit.[24] mp 118–119 °C.

^{1}H NMR (DMSO-d_6): δ = 3.79 (s, 3 H, OCH_3), 6.68 (m, 2 H, NH_2), 7.79 (s, 1 H, H_6), 7.99 (s, 1 H, H_2).

IR (KBr): ν = 3450, 3310, 3180, 1660, 1610, 1590 cm^{-1}.

MS (CI): m/z = 126 (M^+).

5-Azido-6-chloro-2,4-dimethoxypyrimidine (19):
BuLi (0.54 mL, 1.26 mmol) was slowly added to a cold (− 75 °C) solution of 6-chloro-2,4-dimethoxypyrimidine (**18**, 0.2 g, 1.15 mmol) in anhyd THF (30 mL). The resulting solution was stirred 10 min at − 75 °C before addition of TsN_3 (0.25 g, 1.26 mmol) in THF (10 mL). The solution was stirred for 2 h at − 75 °C, then warmed slowly to r.t. Then sat $NaHCO_3$ was added (to pH = 8). Extraction with CH_2Cl_2 (3 × 20 mL), drying ($MgSO_4$) and removal of solvent afforded a crude product which was purified by flash chromatography on silica gel (15 g; eluent: CH_2Cl_2/cyclohexane, 6 : 4); yield: 0.24 g (97%); mp dec. 50 °C.

^{1}H NMR ($CDCl_3$): δ = 3.91 (s, 3 H, OCH_3), 4.03 (s, 3 H, OCH_3).

IR (KBr): ν = 2120, 2090, 1530, 1460, 1360 cm^{-1}.

$C_6H_6ClN_5O$ (215.62): calc. C 33.42 H 2.81 N 32.49
found 33.54 2.80 32.75

5-Amino-6-chloro-2,4-dimethoxypyrimidine (20):
A solution of **19** (0.819 g, 3.8 mmol), piperidine (0.25 mL, 2.5 mmol) in MeOH was cooled to 10 °C. H_2S was bubbled through the solution for 30 min and the temperature was maintained between 10 and 20 °C. After filtration and removal of the solvent, the crude product was purified by flash chromatography on silica gel (40 g; eluent: CH_2Cl_2/EtOac, 96 : 4); yield: 0.67 g (93%); mp 80 °C.

^{1}H NMR ($CDCl_3$): δ = 3.64 (m, 2 H, NH_2), 3.90 (s, 3 H, OCH_3), 4.01 (s, 3 H, OCH_3).

IR (KBr): ν = 3390, 3310, 2990 cm^{-1}.

MS (EI): $m/z = 189/191$ ($^{35}Cl/^{37}Cl$).

$C_6H_6ClN_5O$ (189.62): calc. C 38.00 H 4.26 N 22.16
found 38.09 4.33 21.80

6-Chloro-2,4-dimethoxy-5-(nicotinoylamino)pyrimidine (21):
A mixture of 2-chloronicotinic acid (0.4 g, 2.6 mmol) in $SOCl_2$ (10 mL) was refluxed for 5 h. After cooling and removal of $SOCl_2$, the oil was dissolved in toluene (10 mL). Evaporation of toluene afforded an oil which was dissolved in CH_2Cl_2 (10 mL). The solution of 2-chloronicotinoyl chloride obtained was slowly added to a solution of **20** (0.4 g, 2.1 mmol) in CH_2Cl_2 (5 mL) during which time the temperature was kept at -5 °C, then increased to r.t. for 2.5 h. Hydrolysis with H_2O (10 mL), extraction with CH_2Cl_2 (2×10 mL), drying ($MgSO_4$) and removal of solvent afforded a crude product, which was purified by flash chromatography on silica gel (35 g; eluent: CH_2Cl_2/EtOAc, 4 : 1); yield: 0.58 g (84%); mp 176 °C.

^{1}H NMR ($CDCl_3$): $\delta = 4.04$ (s, 6H, OCH_3), 7.42 (dd, 1H, $H_{5'}$), 7.77 (s, 1H, NHCO), 8.25 (dd, 1H, $H_{4'}$), 8.54 (dd, 1H, $H_{6'}$), $J_{4',6'} = 2$ Hz, $J_{5',6'} = 4.7$ Hz, $J_{4',5'} = 7.7$ Hz.

IR (KBr): $\nu = 3214, 3002, 1664, 1560, 1516, 1383$ cm^{-1}.

MS (EI): $m/z = 328/330$ ($^{35}Cl/^{37}Cl$).

$C_{12}H_{10}Cl_2N_3O_4$ (329.16): calc. C 43.78 H 3.07 N 17.03
found 43.61 3.01 16.97

6-(Cyclopropylamino)-2,4-dimethoxy-5-(nicotinoylamino)pyrimidine (22):
A mixture of **21** (0.1 g, 0.3 mmol), NEt_3 (0.05 mL, 0.36 mmol), cyclopropylamine (0.02 mL, 0.03 mmol) and butanol (10 mL) was warmed in a pressure vessel at 60 °C for 5 days (under a pressure of 25 bar). Cooling and removal of solvent afforded **22** which was purified on silica gel (8 g; eluent: cyclohexane/EtOAc, 8 : 2); yield: 0.079 g (76%); mp 185 °C.

^{1}H NMR ($CDCl_3$): $\delta = 0.5$ (m, 2H), 0.75 (m, 2H), 2.64 (m, 1H, CH), 3.90 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 5.57 (s, 1H, NH), 7.34 (dd, 1H, $H_{5'}$), 7.76 (s, 1H, NHCO), 8.08 (dd, 1H, $H_{4'}$), 8.44 (dd, 1H, $H_{6'}$), $J_{4',5'} = 7.2$ Hz, $J_{5',6'} = 4.8$ Hz, $J_{4',6'} = 2$ Hz.

IR (KBr): $\nu = 3435, 3250, 3001, 2956, 1645, 1598, 1473, 1307$ cm^{-1}.

$C_{15}H_{16}ClN_5O_3$ (349.81): calc. C 51.50 H 4.62 N 20.03
found 51.83 4.62 19.66

11-Cyclopropyl-5,11-dihydro-2,4-dimethoxy-6*H*-pyrido[2,3-*e*]pyrimido[5,4-*b*][1,4]-diazepin-6-one (23)
To an oven-dried, 50 mL, round-bottomed flask under Ar was added NaH (80% dispersion in mineral oil, 0.086 g, 2.87 mmol), cyclohexane (5 mL). After stirring, the supernatant liquid was removed, then diglyme (10 mL) and **22** (0.234 g, 0.67 mmol) were added. The solution was kept under anhyd Ar and slowly heated to 140 °C for 1 h. After cooling, the mixture was poured on ice (10 g) and extracted with EtOAc (3×20 mL). Drying ($MgSO_4$) and removal of solvent afforded a crude product, which was purified by flash chromatography on silica gel (10 g, eluent: cyclohexane/EtOAc, 7 : 3); yield: 0.071 g (34%); mp 186 °C.

^{1}H NMR ($CDCl_3$): $\delta = 0.50$ (m, 2H), 0.98 (m, 2H), 3.59 (m, 1H, CH), 3.96 (s, 3H, OCH_3), 4.00 (s, 3H, OCH_3), 7.07 (dd, 1H, H_8), 7.43 (s, 1H, NHCO), 8.16 (dd, 1H, H_7), 8.50 (dd, 1H, H_9), $J_{7,8} = 7.2$ Hz, $J_{8,9} = 4.8$ Hz, $J_{7,9} = 2$ Hz.

IR (KBr): $\nu = 3247, 3095, 3031, 2946, 1661, 1582, 1560, 1477, 1413, 1360$ cm^{-1}.

MS (EI): $m/z = 313$ (M).

$C_{15}H_{15}N_5O_3$ (313.30): calc. C 57.50 H 4.83 N 22.35
found 57.72 4.62 22.06

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