Reactivity of the Pyrimidine Nitrogen Atom toward an Acetal Moiety: Formation of 3-Ethoxy-2,3-dihydroimidazo[1,2-*c*]pyrimidines by Intramolecular Cyclization of *N*-(2,2-Diethoxyethyl)pyrimidine-4-amines

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Abstract: A new protocol was developed for the synthesis of 2,3-dihydroimidazo[1,2-*c*]pyrimidines, based on an intramolecular reaction between a pyrimidine nitrogen atom and an acetal moiety in the presence of boron trifluoride etherate. The method was expanded to permit the synthesis of the triheterocyclic imidazo[1,2-*c*]pyrazolo[4,3-*e*]pyrimidine system.

Key words: acetals, cyclizations, heterocycles, polycycles, pyrimidines, imidazoles

The chemistry of heterocycles can be very useful, and it has long been studied in detail. As a result of the extensive use of various heterocyclic derivatives in pharmacology,[1] in light-emitting technologies,[2] or as dyes,[3] there is great interest in this branch of chemistry. A search for novel, more efficient, synthetic paths to heterocycles and their functionalized derivatives is crucial for the development of the aforementioned technologies and of heterocyclic chemistry itself.

Fused heterocyclic systems containing the 2,3-dihydroimidazo[1,2-*c*]pyrimidine scaffold exhibit a diversity of biological activities. Such compounds are known to display antipsychotic,[4] antidepressant,[5] antihypertensive,[6] and antiparasitic[7] activities, and they are useful as adenosine receptors antagonists[8] or for treatment of cancer.[9] Recently, 2,3-dihydroimidazo[1,2-*c*]pyrimidine derivatives have been found to exhibit antimycobacterial activities.[10] The main method that is used for the synthesis of these compounds involves the intramolecular cyclization of 4-[(2-hydroxyethyl)amino]pyrimidines in the presence of a chlorinating agent.[5,10,11] Other methods[4,6] for the formation of a 2,3-dihydroimidazole ring on an existing pyrimidine framework are scarce and they are limited to the formation of derivatives bearing alkyl or aryl groups on the carbon atoms of the imidazole ring.

The acetal scaffold is usually used in organic synthesis as means of protecting a carbonyl group or as a precursor of this group. In the absence of an external nucleophile, however, an acetal group can participate in intramolecular cyclization reactions. If an acetal group is present on a side chain in a position adjacent to a pyridine-type nitrogen atom, a cyclization reaction can occur to afford fused heterocycles containing *N*,*O*-acetal fragments. This reaction should unlock a potential for further functionalization of the newly formed ring. However, only a few examples of this type of reaction have been described.[12] Here, we report a novel method for the synthesis of 2,3-dihydroimidazo[1,2-*c*]pyrimidines by the intramolecular reaction between the pyrimidine nitrogen atom and the acetal group in *N*-(2,2-diethoxyethyl)pyrimidine-4-amines.

Generally, we introduced an acetal moiety by nucleophilic substitution of chlorine in chloropyrimidines by (2,2-diethoxyethyl)amine. Thus, pyrimidine **2a**, prepared from the dichloropyrimidine **1**, was treated with dimethylamine to afford the dimethylamino derivative **2b**, whereas the methoxy analogue **2c** was similarly prepared from pyrimidine **3**. Treatment of pyrimidines **2a** and **2c** with boron trifluoride etherate in dichloromethane, followed by a work-up with an aqueous sodium bicarbonate solution gave the corresponding aldehydes **4a** and **4c**. Spectroscopic (NMR and HRMS) and elemental analyses of these compounds were consistent with the proposed structures. In the IR spectra of **4a** and **4c**, instead of one strong absorption band for the carbonyl group, two absorption bands of medium intensity were observed in the region 1710−1750 cm^{-1}. Under the same reaction conditions, the dimethylamino derivative **2b** gave the desired 2,3-dihydroimidazo[1,2-*c*]pyrimidine **5b** (Scheme 1). We found that 2.5 equivalents of boron trifluoride etherate were required to achieve full conversion of compounds **2a**−**c** in the two reactions. In an attempt to prevent the formation of aldehydes, we examined a variety of nonaqueous work-up conditions using bases as such as carbonates, potassium phosphate, or amines, but with no success.

To determine whether the aldehydes **4a**−**c** were formed during the isolation procedure or whether, in fact, no cyclization involving a pyrimidine nitrogen atom had occurred, we attempted to isolate the 2,3-dihydroimidazo[1,2-*c*]pyrimidinium salt intermediates. The reaction conditions for the reactions of **2a**−**c** with boron trifluoride were the same as those described above. After the cyclization had occurred (as determined by thin-layer chromatography), the solvent was removed and salts **6a**−**c** were precipitated with diethyl ether (Scheme 2). NMR spectra of these compounds were recorded in acetonitrile-d_3, as they were unstable in DMSO-d_6. The presence of two peaks at −151.69 ppm and −151.75 ppm in the ^{19}F NMR spectra of **6a**−**c** suggested that the counterion was tetra-

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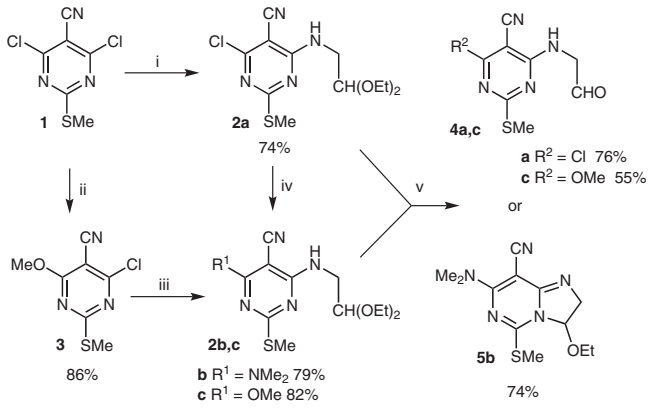
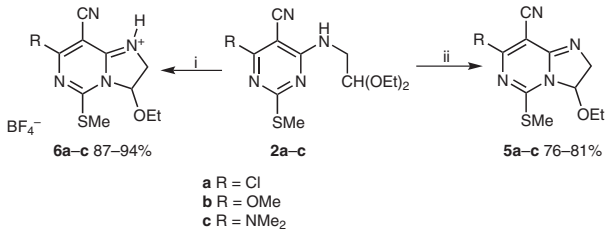


Scheme 1 *Reagents and conditions*: (i) $NH_2CH_2CH(OEt)_2$, Na_2CO_3, MeOH, r.t., 1 h; (ii) MeOH, Na_2CO_3, r.t., 2 h; (iii) $NH_2CH_2CH(OEt)_2$, Et_3N, MeOH, r.t., 20 h; (iv) Me_2NH, *i*-PrOH, r.t., 1.5 h; (v) $BF_3{\cdot}OEt_2$, CH_2Cl_2; then aq $NaHCO_3$.

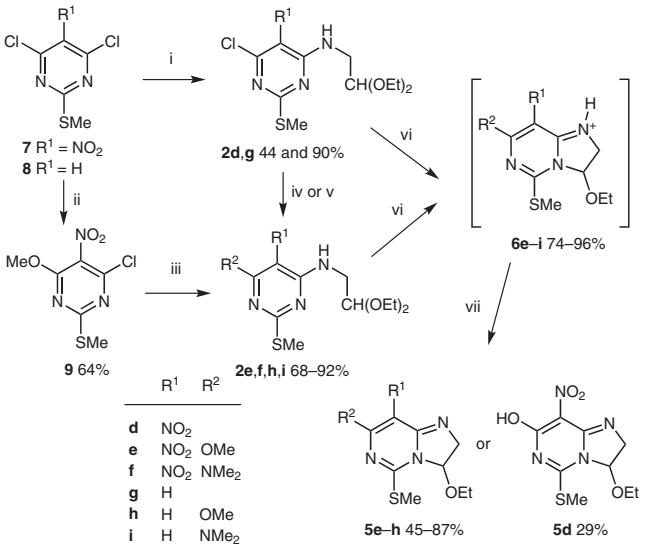
fluoroborate. The isotope shift was 60 ppb, and the ratio of the intensities of the two peaks was 4:1. The presence of isotopomers of tetrafluoroborate has been reported in some earlier cases.[13] Treatment of salts **6a**–**c** with a non-aqueous base (DBU, Et_3N, K_3PO_4, or a carbonate) led to the formation of the corresponding 2,3-dihydroimidazo[1,2-*c*]pyrimidines **5a**–**c**. However, pure compounds could not be obtained by using this isolation procedure. Trituration of solutions of these compounds with water appeared to be essential for the isolation of pure substances. Because workup of the reaction mixtures with aqueous sodium bicarbonate gave aldehydes in some cases, strongly alkaline solutions were used to deprotonate the 2,3-dihydroimidazo[1,2-*c*]pyrimidinium salts in the workup phase. This procedure led to the isolation of the required 2,3-dihydroimidazo[1,2-*c*]pyrimidines **5a**–**c** in good yields. The basicity of the workup solutions therefore appears to be the key factor in determining the course of the reaction.



Scheme 2 *Reagents and conditions*: (i) $BF_3{\cdot}OEt_2$, CH_2Cl_2; (ii) $BF_3{\cdot}OEt_2$, CH_2Cl_2; then 5% aq NaOH.

To explore the scope of the reaction, we synthesized a series of *N*-(2,2-diethoxyethyl)pyrimidin-4-amines **2d**–**i** (Scheme 3, Table 1). Nitro-group-containing pyrimidines **2d**–**f** were chosen for several reasons. As an electron-withdrawing substituent, the nitro group should reduce the reactivity of the pyrimidine nitrogen atom. Also, intermediate salts were expected to be less stable. On the other hand, the target 2,3-dihydroimidazo[1,2-*c*]pyrimidines, as *N*,*O*-acetals, should be stable, as it is known that electron acceptors, such as acyl groups, on the nitrogen atom stabilize *N*,*O*-acetals.[14]

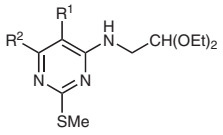
Treatment of pyrimidines **2e**–**i** with boron trifluoride gave the corresponding 2,3-dihydroimidazo[1,2-*c*]pyrimidinium salts **6e**–**i** in good to excellent yields (Scheme 3, Table 1). Attempts to isolate the 7-chloro-3-ethoxy-5-(methylsulfanyl)-8-nitro-2,3-dihydroimidazo[1,2-*c*]pyrimidin-1-ium salt formed in the reaction of **2d** with boron trifluoride resulted in a complex mixture of compounds. Nevertheless, workup with aqueous sodium hydroxide without isolation of the salt gave 3-ethoxy-5-(methylsulfanyl)-8-nitro-2,3-dihydroimidazo[1,2-*c*]pyrimidin-7-ol (**5d**) in low yield. The target compounds **5e**–**h** can therefore be obtained either from the isolated 2,3-dihydroimidazo[1,2-*c*]pyrimidinium salts **6e**–**h** or directly from the pyrimidines **2e**–**h**. Note that 2,3-dihydroimidazo[1,2-*c*]pyrimidines **5e**–**h** were obtained in better yields (for example, **5b** was isolated in a 12% greater yield) when they were synthesized without isolation of the intermediate salts. However, all attempts to isolate 3-ethoxy-*N*,*N*-dimethyl-5-(methylsulfanyl)-2,3-dihydroimidazo[1,2-*c*]pyrimidin-7-amine by normal- or reverse-phase chromatography or by crystallization resulted in failure.



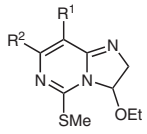
Scheme 3 *Reagents and conditions*: (i) for $R^1 = NO_2$: $NH_2CH_2CH(OEt)_2$, Na_2CO_3, *i*-PrOH, r.t., 5 min; for $R^1 = H$: $NH_2CH_2CH(OEt)_2$, Et_3N, *i*-PrOH, 60–65 °C, 3 h; (ii) MeOH, Na_2CO_3, r.t., 5 h; (iii) $NH_2CH_2CH(OEt)_2$, Et_3N, *i*-PrOH, r.t. (iv) NaOMe, MeOH, 100 °C, 16 h; (v) for $R^1 = NO_2$: Me_2NH, *i*-PrOH, r.t., 15 min; for $R^1 = H$: Me_2NH, 1,4-dioxane, 100 °C, 6 h; (vi) $BF_3{\cdot}OEt_2$, CH_2Cl_2; (vii) 5% aq NaOH.

The nature of the substituent at the 6-position of the pyrimidine had a marked effect on the reaction time. Compounds containing a chlorine group reacted within several minutes, whereas full conversion of pyrimidines bearing a dimethylamino group required two hours (Table 1, entries 2, 6, 9). These results were opposite to those expected. It appears that the pyrimidine nitrogen atom in the dimethylamino derivatives is not only more nucleophilic than

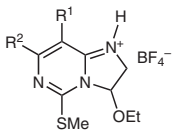
Table 1 Preparation of *N*-(2,2-Diethoxyethyl)pyrimidine-4-amines **2a**–**i** and 2,3-Dihydroimidazo[1,2-*c*]pyrimidines **5a**–**h** and Their Salts **6a**–**c** and **6e**–**i**



2a–k



5a–c,e–h,j,k

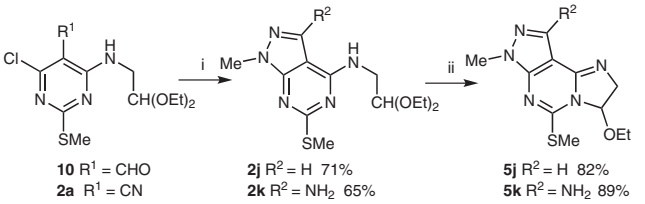


6a–c,e–i

Entry	R^1	R^2	Yield (%) of **2**	Yield (%) of **5**	Yield (%) of **6**	Time (for **5** and **6**)
1	CN	Cl	**2a** 74	**5a** 81	**6a** 94	10 min
2	CN	NMe_2	**2b** 79	**5b** 76	**6b** 97	2 h
3	CN	OMe	**2c** 82	**5c** 79	**6c** 87	1.5 h
4	NO_2	Cl	**2d** 44	**5d** 29	–	5 min
5	NO_2	OMe	**2e** 69	**5e** 87	**6e** 96	1 h
6	NO_2	NMe_2	**2f** 68	**5f** 78	**6f** 96	2 h
7	H	Cl	**2g** 90	**5g** 50	**6g** 96	10 min
8	H	OMe	**2h** 72	**5h** 45	**6h** 74	1 h
9	H	NMe_2	**2i** 92	–	**6i** 95	2 h

that in the chloro compounds, but also more basic, so that its interaction with boron trifluoride retards the reaction. On the other hand, substituents at the 5-position of the pyrimidine did not have a significant effect on the reaction time; however, lower yields of the 2,3-dihydroimidazo[1,2-*c*]pyrimidines **5g** and **5h** were obtained from the 5-unsubstituted pyrimidines **2g** and **2h** (Table 1, entries 7, 8).

Note that 2,3-dihydroimidazo[1,2-*c*]pyrimidines **5a**–**h** are unstable when stored at room temperature. Decomposition occurs within hours or days, depending on the structure of the particular compound. Because of this low stability of the synthesized 2,3-dihydroimidazo[1,2-*c*]pyrimidines, we decided to use another heterocyclic scaffold in the reaction. On the basis of our previous work,[15] we synthesized two pyrazolo[3,4-*d*]pyrimidines **2j** and **2k** containing a (2,2-diethoxyethyl)amino group at the 4-position of the pyrazolopyrimidine moiety by the reaction of the corresponding 6-chloropyrimidines **2a** and **10** with an excess of methylhydrazine (Scheme 4). The conversion of **2j** and **2k** into the corresponding dihydroimidazo[1,2-*c*]pyrazolo[4,3-*e*]pyrimidines **5j** and **5k** was carried out under the same reaction conditions as those used for the synthesis of compounds **5a**–**h**. In contrast to the 2,3-dihydroimidazo[1,2-*c*]pyrimidines **5a**–**h**, compounds **5j** and **5k** appeared to be stable for weeks or more when stored at room temperature.



10 R^1 = CHO
2a R^1 = CN

2j R^2 = H 71%
2k R^2 = NH_2 65%

5j R^2 = H 82%
5k R^2 = NH_2 89%

Scheme 4 *Reagents and conditions*: (i) $MeNHNH_2$, *i*-PrOH, 30 min; (ii) $BF_3{\cdot}OEt_2$, CH_2Cl_2, 2 h; then 5% aq NaOH.

In summary, we have developed a novel method for the synthesis of 2,3-dihydroimidazo[1,2-*c*]pyrimidines by intramolecular cyclization of *N*-(2,2-diethoxyethyl)pyrimidin-4-amines. The use of strongly basic aqueous solutions in the reaction workup is essential for the deprotonation of intermediate 2,3-dihydroimidazo[1,2-*c*]pyrimidinium tetrafluoroborate salts. The reaction can also be used in the synthesis of tricyclic heterocycles containing imidazopyrimidine moieties.

Melting points were determined in open capillaries by using a digital melting point apparatus (IA9100 Series; Electrothermal) and are uncorrected. IR spectra were recorded on a FTIR spectrophotometer (Spectrum BX II; PerkinElmer) in KBr unless stated otherwise. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Unity Inova spectrometer at 300 MHz and 75 MHz, respectively, for all compounds except **4a** and **4c**; residual solvents signals were used as internal standard. ^{1}H NMR and ^{13}C NMR spectra for compounds **4a** and **4c** were recorded on a Bruker Ascend 400 spectrometer (400 MHz and 100 MHz, respectively) with residual solvent signals as internal standards. All reactions and purities of the synthesized compounds were monitored by TLC on silica gel 60 F254-coated aluminum plates (Merck) with visualization by UV radiation. Elemental analyses were performed on a Thermo Scientific FLASH 2000 apparatus. HRMS data were obtained with an Agilent 6230 TOF mass spectrometer (ESI).

4-Chloro-6-[(2,2-diethoxyethyl)amino]-2-(methylsulfanyl)pyrimidine-5-carbonitrile (2a)

A suspension of pyrimidine **1**[16] (0.5 g, 2.27 mmol) in MeOH (25 mL) was treated by dropwise addition of a soln of 2,2-diethoxyethylamine (395 μL, 23 mmol) in MeOH (5 mL). Na_2CO_3 (0.29 g, 2.73 mmol) was added and the mixture was stirred at r.t. for 1 h. H_2O (100 mL) was then added and the resulting precipitate was collected by filtration, dried, and crystallized (hexane) to give a colorless solid; yield: 0.53 g (74%); mp 74–75 °C.

IR (KBr): 3332 (NH), 2222 (CN) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.28 (t, J = 6.9 Hz, 6 H, 2 × CH_3), 2.56 (s, 3 H, SCH_3), 3.60 (dq, ^2J = 9.6 Hz, ^3J = 6.9 Hz, 2 H, 2 × $CH_AH_BCH_3$), 3.70–3.84 (m, 4 H, NCH_2 and 2 × $CH_AH_BCH_3$), 4.64 (t, J = 5.4 Hz, 1 H, OCH), 5.89 (t, J = 5.4 Hz, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.7, 15.6, 44.0, 63.5, 86.1, 100.2, 113.8, 161.2, 161.5, 176.3.

Anal. Calcd for $C_{12}H_{17}ClN_4O_2S$: C, 45.49; H, 5.41; found: C, 45.62; H, 5.57.

4-[(2,2-Diethoxyethyl)amino]-6-(dimethylamino)-2-(methylsulfanyl)pyrimidine-5-carbonitrile (2b)

40% aq Me_2NH (748 μL, 6.0 mmol) was added to a suspension of pyrimidine **2a** (0.76 g, 2.4 mmol) in *i*-PrOH (20 mL), and the mixture was stirred at r.t. for 1.5 h. H_2O (100 mL) was added and the precipitate was collected by filtration, dried, and crystallized (hexane) to give a colorless solid; yield: 0.45 g (79%); mp 86–87 °C.

IR (KBr): 3326, 3300 (NH), 2204 (CN) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.26 (t, *J* = 7.2 Hz, 6 H, 2 × CH_3), 2.48 (s, 3 H, SCH_3), 3.31 [s, 6 H, $N(CH_3)_2$], 3.59 (dq, ^2J = 9.6 Hz, ^3J = 7.2 Hz, 2 H, 2 × C$H_A$$H_B$$CH_3$), 3.66 (t, *J* = 5.7 Hz, 2 H, NCH_2), 3.76 (dq, ^2J = 9.6 Hz, ^3J = 7.2 Hz, 2 H, 2 × $CH_A$$H_B$$CH_3$), 4.60 (t, *J* = 5.7 Hz, 1 H, OCH), 5.66 (t, *J* = 5.7 Hz, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.3, 15.6, 39.7, 43.8, 63.2, 65.5, 101.0, 119.1, 161.2, 163.9, 173.3.

Anal. Calcd for $C_{14}H_{23}N_5O_2S$: C, 51.67; H, 7.12. Found: C, 52.09; H, 7.15.

4-[(2,2-Diethoxyethyl)amino]-6-methoxy-2-(methylsulfanyl)pyrimidine-5-carbonitrile (2c)

2,2-Diethoxyethylamine (505 μL, 3.48 mmol) and Et_3N (485 μL, 3.48 mmol) were added to a soln of pyrimidine **3** (0.5 g, 2.32 mmol) in MeOH (25 mL), and the mixture was stirred at r.t. for 20 h. H_2O (100 mL) was added and the precipitate was collected by filtration, dried, and crystallized (hexane) to give a colorless solid; yield: 0.62 g (82%); mp 84–85 °C.

IR (KBr): 3320 (NH), 2220 (CN) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.26 (t, *J* = 6.9 Hz, 6 H, 2 × CH_3), 2.53 (s, 3 H, SCH_3), 3.58 (dq, ^2J = 9.6 Hz, ^3J = 6.9 Hz, 2 H, 2 × C$H_A$$H_B$$CH_3$), 3.69 (t, *J* = 5.4 Hz, 2 H, NCH_2), 3.76 (dq, ^2J = 9.6 Hz, ^3J = 6.9 Hz, 2 H, 2 × $CH_A$$H_B$$CH_3$), 4.02 (s, 3 H, OCH_3), 4.61 (t, *J* = 5.4 Hz, 1 H, OCH), 5.65 (t, *J* = 5.4 Hz, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.5, 15.6, 43.8, 54.9, 63.3, 70.6, 100.7, 114.7, 162.8, 169.7, 175.6.

Anal. Calcd for $C_{13}H_{20}N_4O_3S$: C, 49.98; H, 6.45. Found: C, 50.08; H, 6.59.

6-Chloro-*N*-(2,2-diethoxyethyl)-2-(methylsulfanyl)-5-nitropyrimidin-4-amine (2d)

2,2-Diethoxyethylamine (430 μL, 2.95 mmol) and Na_2CO_3 (0.285 g, 2.69 mmol) were added to a stirred soln of pyrimidine **7**[17] (0.645 g, 2.69 mmol) in *i*-PrOH (20 mL). After 5 min, H_2O (50 mL) was added and the product was extracted with CH_2Cl_2 (2 × 50 mL). The organic layers were combined, washed with H_2O (2 × 20 mL), dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography [silica gel, hexane–benzene (1:1); R_f = 0.15] to give a yellow solid; yield: 0.40 g (44%); mp 71.5–73.5 °C.

IR (KBr): 3364 (NH) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.28 (t, *J* = 7.2 Hz, 6 H, 2 × CH_3), 2.58 (s, 3 H, SCH_3), 3.61 (dq, ^2J = 9.3 Hz, ^3J = 7.2 Hz, 2 H, 2 × C$H_A$$H_B$$CH_3$), 3.73–3.85 (m, 4 H, NCH_2 and 2 × $CH_A$$H_B$$CH_3$), 4.69 (t, *J* = 5.4 Hz, 1 H, OCH), 8.17 (br s, 1 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 14.5, 15.7, 44.3, 62.3, 99.8, 124.6, 152.6, 154.6, 173.0.

Anal. Calcd for $C_{11}H_{17}ClN_4O_4S$: C, 39.23; H, 5.09. Found: C, 39.21; H, 5.07.

***N*-(2,2-Diethoxyethyl)-6-methoxy-2-(methylsulfanyl)-5-nitropyrimidin-4-amine (2e)**

2,2-Diethoxyethylamine (470 μL, 3.23 mmol) was added to a suspension of pyrimidine **9** (0.63 g, 2.67 mmol) in *i*-PrOH (30 mL), and the mixture was stirred at r.t. until the starting compound has dissolved. Et_3N (560 μL, 4.0 mmol) was then added and the mixture was stirred for a further 45 min. H_2O (50 mL) was added and the product was extracted with CH_2Cl_2 (2 × 50 mL). The organic layers were combined, washed with H_2O (2 × 20 mL), dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography (silica gel, CH_2Cl_2; R_f = 0.42) to give a yellow solid; yield: 0.61 g (69%); mp 65.5–67.5 °C.

IR (KBr): 3380 (NH) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.27 (t, *J* = 6.9 Hz, 6 H, 2 × CH_3), 2.55 (s, 3 H, SCH_3), 3.60 (dq, ^2J = 9.3 Hz, ^3J = 6.9 Hz, 2 H, 2 × C$H_A$$H_B$$CH_3$), 3.72–3.83 (m, 4 H, NCH_2 and 2 × $CH_A$$H_B$$CH_3$), 4.09 (s, 3 H, OCH_3), 4.68 (t, *J* = 5.4 Hz, 1 H, OCH), 8.84 (br s, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.8, 15.6, 44.3, 55.7, 63.2, 100.5, 113.5, 156.6, 163.8, 174.6.

Anal. Calcd for $C_{12}H_{20}N_4O_5S$: C, 43.36; H, 6.07. Found: C, 43.68; H, 6.11.

***N*′-(2,2-Diethoxyethyl)-*N*,*N*-dimethyl-2-(methylsulfanyl)-5-nitropyrimidine-4,6-diamine (2f)**

40% aq Me_2NH (340 μL, 2.73 mmol) was added to a suspension of pyrimidine **2d** (0.40 g, 1.19 mmol) in *i*-PrOH (15 mL), and the mixture was stirred at r.t. until the starting compound has dissolved (~15 min). H_2O (50 mL) was added and the product was extracted with CH_2Cl_2 (2 × 50 mL). The organic layers were combined, washed with H_2O (2 × 20 mL), dried (Na_2SO_4), and concentrated. The crude product was crystallized from hexane at –15 °C to give a yellow solid; yield: 0.28 g (68%); mp 46–47 °C.

IR (KBr): 3368 (NH) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.27 (t, *J* = 6.9 Hz, 6 H, 2 × CH_3), 2.51 (s, 3 H, SCH_3), 3.10 [s, 6 H, $N(CH_3)_2$], 3.61 (dq, ^2J = 9.3 Hz, ^3J = 6.9 Hz, 2 H, 2 × C$H_A$$H_B$$CH_3$), 3.71–3.82 (m, 4 H, NCH_2 and 2 × $CH_A$$H_B$$CH_3$), 4.67 (t, *J* = 5.4 Hz, 1 H, OCH), 8.60 (br s, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.7, 15.6, 40.6, 44.1, 63.1, 100.8, 111.7, 156.5, 158.2, 172.5.

Anal. Calcd for $C_{13}H_{23}N_5O_4S$: C, 45.20; H, 6.71. Found: C, 45.30; H, 6.67.

6-Chloro-*N*-(2,2-diethoxyethyl)-2-(methylsulfanyl)pyrimidin-4-amine (2g)

2,2-Diethoxyethylamine (3.35 mL, 23 mmol) and Et_3N (3.2 mL, 23 mmol) were added to a suspension of pyrimidine **8**[18] (3.0 g, 15.4 mmol) in *i*-PrOH (50 mL), and the mixture was heated in the sand bath at 60–65 °C for 3 h. H_2O (200 mL) was added and the precipitate was collected by filtration, dried, and crystallized (hexane) to give a colorless solid; yield: 4.05 g (90%); mp 76–77 °C.

IR (KBr): 3324 (NH) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.26 (t, *J* = 6.9 Hz, 6 H, 2 × CH_3), 2.53 (s, 3 H, SCH_3), 3.45–3.64 (m, 4 H, NCH_2 and 2 × C$H_A$$H_B$$CH_3$), 3.75 (dq, ^2J = 9.6 Hz, ^3J = 6.9 Hz, 2 H, 2 × $CH_A$$H_B$$CH_3$), 4.62 (t, *J* = 5.1 Hz, 1 H, OCH), 5.21 (br s, 1 H, NH), 6.11 (s, 1 H, Ar-H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 14.1, 16.0, 43.5, 62.5, 99.9, 100.5, 157.3, 163.3, 171.9.

Anal. Calcd for $C_{11}H_{18}ClN_3O_2S$: C, 45.28; H, 6.22. Found: C, 45.48; H, 6.52.

***N*-(2,2-Diethoxyethyl)-6-methoxy-2-(methylsulfanyl)pyrimidin-4-amine (2h)**

A mixture of pyrimidine **2g** (0.4 g, 1.37 mmol), NaOMe (0.37 g, 6.85 mmol), and MeOH (10 mL) was heated at 100 °C in a closed pressure vessel for 16 h, then cooled to r.t. H_2O (40 mL) was added and the product was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with H_2O (2 × 20 mL), dried (Na_2SO_4), and concentrated. The product was purified by flash chromatography [silica gel, PE–EtOAc (9:1); R_f = 0.46] to give a pinkish oil; yield: 0.28 g (72%).

IR (CH_2Cl_2 film): 3383 (NH) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.24 (t, *J* = 6.9 Hz, 6 H, 2 × CH_3), 2.52 (s, 3 H, SCH_3), 3.42 (t, *J* = 5.4 Hz, 2 H, NCH_2), 3.57 (dq, ^2J = 9.6 Hz, ^3J = 6.9 Hz, 2 H, 2 × C$H_A$$H_B$$CH_3$), 3.73 (dq, ^2J = 9.6

Hz, ^3J = 6.9 Hz, 2 H, 2 × $CH_AH_BCH_3$), 3.91 (s, 3 H, OCH_3), 4.62 (t, J = 5.4 Hz, 1 H, OCH), 5.08 (br s, 1 H, NH), 5.42 (s, 1 H, Ar-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2, 15.6, 44.2, 53.8, 63.0, 81.3, 100.9, 163.9, 170.1, 170.9.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{12}H_{22}N_3O_3S$: 288.1376; found: 288.1385.

N'-(2,2-Diethoxyethyl)-N,N-dimethyl-2-(methylsulfanyl)pyrimidine-4,6-diamine (2i)

A mixture of pyrimidine **2g** (0.5 g, 1.71 mmol), 40% aq Me_2NH (3 mL, 24 mmol), and 1,4-dioxane (8 mL) was heated at 100 °C in a closed pressure vessel for 6 h. H_2O (40 mL) was added and the resulting precipitate was collected by filtration and dried to give an analytically pure colorless solid; yield: 0.47 g (92%); mp 94.5–96 °C.

IR (KBr): 3271 (NH) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26 (t, J = 6.9 Hz, 6 H, 2 × CH_3), 2.51 (s, 3 H, SCH_3), 3.07 [s, 6 H, $N(CH_3)_2$], 3.42 (t, J = 5.4 Hz, 2 H, NCH_2), 3.59 (dq, ^2J = 9.3 Hz, ^3J = 6.9 Hz, 2 H, 2 × $CH_AH_BCH_3$), 3.75 (dq, ^2J = 9.3 Hz, ^3J = 6.9 Hz, 2 H, 2 × $CH_AH_BCH_3$), 4.65 (t, J = 5.4 Hz, 1 H, OCH), 4.76 (br s, 1 H, NH), 5.12 (s, 1 H, Ar-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 15.6, 33.3, 44.3, 63.8, 76.8, 101.2, 163.0 (C-4, C-6, from HMBC data), 169.9.

Anal. Calcd for $C_{13}H_{24}N_4O_2S$: C, 51.97; H, 8.05. Found: C, 52.01; H, 8.05.

***N*-(2,2-Diethoxyethyl)-1-methyl-6-(methylsulfanyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (2j)**

$MeNHNH_2$ (1.25 mL, 23.6 mmol) was added to a soln of pyrimidine **10** (3.0 g, 9.38 mmol) in *i*-PrOH (100 mL), and the mixture was stirred at r.t. for 30 min. The solvent was evaporated under reduced pressure, and the product was extracted with CH_2Cl_2 (30 mL). The soln was washed with H_2O (2 × 20 mL), dried (Na_2SO_4), and flushed through a 1-cm-thick layer of silica gel with CH_2Cl_2. After a removal of the solvent, the residue was crystallized (hexane) to give a colorless solid; yield: 2.07 g (71%); mp 81–82.5 °C.

IR (KBr): 3302 (NH) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.27 (t, J = 6.9 Hz, 6 H, 2 × CH_3), 2.61 (s, 3 H, SCH_3), 3.62 (dq, ^2J = 9.3 Hz, ^3J = 6.9 Hz, 2 H, 2 × $CH_AH_BCH_3$), 3.72–3.84 (m, 4 H, NCH_2 and 2 × $CH_AH_BCH_3$), 3.98 (s, 3 H, NCH_3), 4.72 (t, J = 5.1 Hz, 1 H, OCH), 5.60 (br s, 1 H, NH), 7.81 (s, 1 H, Ar-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.4, 15.6, 33.9, 43.4, 63.2, 98.7, 100.8, 130.5, 154.5, 156.1, 169.7.

Anal. Calcd for $C_{13}H_{21}N_5O_2S$: C, 50.14; H, 6.80. Found: C, 50.37; H, 6.68.

***N*^{4}-(2,2-Diethoxyethyl)-1-methyl-6-(methylsulfanyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine-3,4-diamine (2k)**

$MeNHNH_2$ (126 μL, 2.34 mmol) was added to a suspension of pyrimidine **2a** (0.30 g, 0.95 mmol) in *i*-PrOH (10 mL), and the mixture was refluxed for 30 min. H_2O (40 mL) was then added and the resulting precipitate was collected by filtration, dried, and crystallized (MeOH) to give a colorless solid; yield: 0.20 g (65%); mp 179–180 °C.

IR (KBr): 3422, 3382, 3300, 3208 (NH, NH_2) cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.13 (t, J = 6.9 Hz, 6 H, 2 × CH_3), 2.48 (s, 3 H, SCH_3), 3.48–3.56 (m, 4 H, NCH_2 and 2 × $CH_AH_BCH_3$), 3.57 (s, 3 H, NCH_3), 3.68 (dq, ^2J = 9.6 Hz, ^3J = 6.9 Hz, 2 H, 2 × $CH_AH_BCH_3$), 4.73 (t, J = 5.4 Hz, 1 H, CH), 5.69 (s, 2 H, NH_2), 7.46 (t, J = 5.4 Hz, 1 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 14.3, 16.3, 33.2, 44.1, 62.8, 88.4, 101.0, 147.9, 154.5, 156.4, 168.8.

Anal. Calcd for $C_{13}H_{22}N_6O_2S$: C, 47.83; H, 6.79. Found: C, 47.85; H, 6.79.

4-Chloro-6-methoxy-2-(methylsulfanyl)pyrimidine-5-carbonitrile (3)

Et_3N (1.79 mL, 1.30 g, 11.87 mmol) was added dropwise to a suspension of pyrimidine **1** (2.5 g, 11.4 mmol) in MeOH (40 mL), and the mixture was stirred at r.t. for 2 h. H_2O (200 mL) was added and the precipitate was collected by filtration, dried, and crystallized (*i*-PrOH) to give a colorless solid; yield: 2.10 g (86%); mp 123–124.5 °C.

IR (KBr): 2229 (CN) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.61 (s, 3 H, SCH_3), 4.14 (s, 3 H, OCH_3).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 14.6, 56.0, 90.7, 112.0, 162.5, 169.1, 176.8.

Anal. Calcd for $C_7H_6ClN_3OS$: C, 38.99; H, 2.80. Found: C, 39.15; H, 2.68.

4-Substituted 2-(Methylsulfanyl)-6-[(2-oxoethyl)amino]pyrimidine-5-carbonitriles 4a and 4c; General Procedure

$BF_3{\cdot}OEt_2$ (95 μL, 0.75 mmol) was added to a soln of pyrimidine **2a** or **2c** (0.30 mmol) in CH_2Cl_2 (5 mL), and the mixture was stirred at r.t. for 5 min (**2a**) or 2 h (**2c**). The mixture was then washed successively with 5% aq $NaHCO_3$ (5 mL) and H_2O (2 × 5 mL). The organic layers were combined, dried (Na_2SO_4) and, without removal of the solvent, purified by flash chromatography.

4-Chloro-2-(methylsulfanyl)-6-[(2-oxoethyl)amino]pyrimidine-5-carbonitrile (4a)

Colorless solid: yield: 55 mg (76%); mp 140 °C (dec.); R_f = 0.1 (CH_2Cl_2).

IR (KBr): 3330 (NH), 2846, 2728 (CHO), 2220 (CN), 1735, 1715 (CO) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.52 (s, 3 H, SCH_3), 4.45 (d, J = 5.2 Hz, 2 H, CH_2), 6.42 (br s, 1 H, NH), 9.74 (s, 1 H, CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.5, 51.4, 86.2, 113.3, 161.10, 161.17, 176.5, 195.0.

Anal. Calcd for $C_8H_7ClN_4OS$: C, 39.59; H, 2.91. Found: C, 39.89; H, 3.03.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_8H_7ClN_4OS$: 243.0102; found: 243.0108.

4-Methoxy-2-(methylsulfanyl)-6-[(2-oxoethyl)amino]pyrimidine-5-carbonitrile (4c)

Colorless solid: yield: 39 mg (55%); mp 160 °C (dec.); R_f = 0.15 (CH_2Cl_2).

IR (KBr): 3332 (NH), 2848, 2741 (CHO), 2213 (CN), 1747, 1713 (CO) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.49 (s, 3 H, SCH_3), 4.04 (s, 3 H, OCH_3), 4.37 (d, J = 5.2 Hz, 2 H, CH_2), 6.22 (br s, 1 H, NH), 9.71 (s, 1 H, CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2, 51.4, 54.9, 70.7, 114.1, 162.5, 169.4, 175.8, 196.5.

Anal. Calcd for $C_9H_{10}N_4O_2S$: C, 45.37; H, 4.23. Found: C, 45.03; H, 4.22.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_9H_{10}N_4O_2S$: 239.0597; found: 239.0605.

3-Ethoxy-2,3-dihydroimidazo[1,2-*c*]pyrimidines 5a–h, 5j, and 5k; General Procedure

$BF_3{\cdot}OEt_2$ (95 μL, 0.75 mmol) was added to a soln of the appropriate 4-(2,2-diethoxyethyl)aminopyrimidine **2a**–**k** (0.30 mmol) in CH_2Cl_2 (5 mL), and the mixture was stirred at r.t. for 10 min to 2 h (TLC monitoring). The mixture was then washed successively with

5% aq NaOH (5 mL) and H_2O (2 × 5 mL). The organic layers were combined, dried (Na_2SO_4) and, without removal of a solvent, purified by flash chromatography. Impurities were eluted with CH_2Cl_2, and the product was eluted with a mixture of CH_2Cl_2 and acetone in the ratio given below.

7-Chloro-3-ethoxy-5-(methylsulfanyl)-2,3-dihydroimidazo[1,2-*c*]pyrimidine-8-carbonitrile (5a)
Reaction time: 10 min. Yellowish oil; yield: 66 mg (81%); R_f = 0.4 (CH_2Cl_2–acetone, 9:1).

IR (KBr): 2224 (CN) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.26 (t, *J* = 6.9 Hz, 3 H, CH_3), 2.65 (s, 3 H, SCH_3), 3.47 (dq, ^2J = 9.0 Hz, ^3J = 6.9 Hz, 1 H, CH_AH$_B$CH$_3$), 3.59 (dq, ^2J = 9.0 Hz, ^3J = 6.9 Hz, 1 H, CH$_A$H$_B$CH$_3$), 3.95 (dd, ^2J = 16.2 Hz, ^3J = 3.3 Hz, 1 H, NCH_AH$_B$CH), 4.05 (dd, ^2J = 16.2 Hz, ^3J = 7.5 Hz, 1 H, NCH$_A$H$_B$CH), 5.70 (dd, ^3J = 7.5 Hz, ^3J = 3.3 Hz, 1 H, CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.4, 15.3, 59.9, 61.9, 88.0, 90.3, 112.9, 150.9, 159.8, 165.5.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{10}H_{12}ClN_4OS$: 271.0415; found: 271.0420.

7-(Dimethylamino)-3-ethoxy-5-(methylsulfanyl)-2,3-dihydroimidazo[1,2-*c*]pyrimidine-8-carbonitrile (5b)
Reaction time: 2 h. Yellowish solid; yield: 66 mg (79%); mp 60 °C (dec.); R_f = 0.25 (CH_2Cl_2–acetone, 1:1).

IR (KBr): 2199 (CN) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.22 (t, *J* = 6.9 Hz, 3 H, CH_3), 2.54 (s, 3 H, SCH_3), 3.35–3.44 [m, 7 H, CH_AH$_B$CH$_3$ and N$(CH_3)_2$], 3.54 (dq, ^2J = 9.0 Hz, ^3J = 6.9 Hz, 1 H, CH$_A$H$_B$CH$_3$), 3.86 (dd, ^2J = 15.9 Hz, ^3J = 2.7 Hz, 1 H, NCH_AH$_B$CH), 4.03 (dd, ^2J = 15.9 Hz, ^3J = 7.2 Hz, 1 H, NCH$_A$H$_B$CH), 5.64 (dd, ^3J = 7.2 Hz ^3J = 2.7 Hz, 1 H, CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 15.3, 40.6, 59.2, 60.6, 61.9, 87.4, 118.4, 155.5, 159.8, 160.7.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{12}H_{18}N_5OS$: 280.1227; found: 280.1232.

Anal. Calcd for $C_{12}H_{17}N_5OS$: C, 51.59; H, 6.13. Found: C, 51.37; H, 6.23.

3-Ethoxy-7-methoxy-5-(methylsulfanyl)-2,3-dihydroimidazo[1,2-*c*]pyrimidine-8-carbonitrile (5c)
Reaction time: 90 min. Yellowish solid; yield: 61 mg (76%); mp 73 °C (dec.); R_f = 0.1 (CH_2Cl_2–acetone, 9:1).

IR (KBr): 2216 (CN) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.25 (t, *J* = 6.9 Hz, 3 H, CH_3), 2.64 (s, 3 H, SCH_3), 3.42 (dq, ^2J = 9.0 Hz, ^3J = 6.9 Hz, 1 H, CH_AH$_B$CH$_3$), 3.57 (dq, ^2J = 9.0 Hz, ^3J = 6.9 Hz, 1 H, CH$_A$H$_B$CH$_3$), 3.93 (dd, ^2J = 16.2 Hz, ^3J = 2.7 Hz, 1 H, NCH_AH$_B$CH), 3.98–4.08 (m, 4 H, NCH$_A$H$_B$CH and OCH$_3$), 5.68 (dd, ^3J = 7.2 Hz ^3J = 2.7 Hz, 1 H, CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 15.3, 55.7, 59.7, 61.1, 69.3, 87.6, 113.9, 153.1, 165.5, 169.1.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{11}H_{15}N_4O_2S$: 267.0910; found: 267.0916.

3-Ethoxy-5-(methylsulfanyl)-8-nitro-2,3-dihydroimidazo[1,2-*c*]pyrimidin-7-ol (5d)
Reaction time: 5 min. Yellow solid; yield: 24 mg (29%); mp 160 °C (dec.); R_f = 0.1 (CH_2Cl_2–acetone, 7:1).

IR (KBr): 3259 (OH), 1649 (C=O) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.16 (t, *J* = 6.9 Hz, 3 H, CH_3), 2.52 (s, 3 H, SCH_3), 3.57 (dq, ^2J = 9.0 Hz, ^3J = 6.9 Hz, 1 H, CH_AH$_B$CH$_3$), 3.65 (dq, ^2J = 9.0 Hz, ^3J = 6.9 Hz, 1 H, CH$_A$H$_B$CH$_3$), 3.81 (dd, ^2J = 12.6 Hz, ^3J = 1.8 Hz, 1 H, NCH_AH$_B$CH), 3.98 (dd, ^2J = 12.6 Hz, ^3J = 6.9 Hz, 1 H, NCH$_A$H$_B$CH), 5.91 (dd, ^3J = 6.9 Hz ^3J = 1.8 Hz, 1 H, CH), 9.88 (s, 1 H, OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 15.3, 50.6, 62.4, 86.4, 111.4, 154.0, 159.5, 159.8.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_9H_{12}N_4O_4S$: 273.0652; found: 273.0657.

3-Ethoxy-7-methoxy-5-(methylsulfanyl)-8-nitro-2,3-dihydroimidazo[1,2-*c*]pyrimidine (5e)
Reaction time: 1 h. Yellow oil; yield: 78 mg (87%); R_f = 0.25 (CH_2Cl_2–acetone, 3:1).

^1H NMR (300 MHz, $CDCl_3$): δ = 1.22 (t, *J* = 6.9 Hz, 3 H, CH_3), 2.65 (s, 3 H, SCH_3), 3.43 (dq, ^2J = 9.0 Hz, ^3J = 6.9 Hz, 1 H, CH_AH$_B$CH$_3$), 3.57 (dq, ^2J = 9.0 Hz, ^3J = 6.9 Hz, 1 H, CH$_A$H$_B$CH$_3$), 4.03 (dd, ^2J = 16.5 Hz, ^3J = 2.7 Hz, 1 H, NCH_AH$_B$CH), 4.08–4.15 (m, 4 H, NCH$_A$H$_B$CH and OCH$_3$), 5.66 (dd, ^3J = 6.9 Hz ^3J = 2.7 Hz, 1 H, CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2, 15.1, 56.1, 60.3, 61.2, 87.3, 112.9, 148.6, 161.7, 164.8.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{10}H_{14}N_4O_4S$: 287.0809; found: 287.0815.

3-Ethoxy-*N*,*N*-dimethyl-5-(methylsulfanyl)-8-nitro-2,3-dihydroimidazo[1,2-*c*]pyrimidin-7-amine (5f)
Reaction time: 2 h. Yellow solid; yield: 68 mg (78%); mp 72 °C (dec.); R_f = 0.25 (CH_2Cl_2–acetone, 1:1).

^1H NMR (300 MHz, $CDCl_3$): δ = 1.17 (t, *J* = 6.9 Hz, 3 H, CH_3), 2.53 (s, 3 H, SCH_3), 3.15 [s, 6 H, N$(CH_3)_2$], 3.38 (dq, ^2J = 9.0 Hz, ^3J = 6.9 Hz, 1 H, CH_AH$_B$CH$_3$), 3.51 (dq, ^2J = 9.0 Hz, ^3J = 6.9 Hz, 1 H, CH$_A$H$_B$CH$_3$), 3.98 (dd, ^2J = 16.5 Hz, ^3J = 2.7 Hz, 1 H, NCH_AH$_B$CH), 4.06 (dd, ^2J = 16.5 Hz, ^3J = 6.6 Hz, 1 H, NCH$_A$H$_B$CH), 5.57 (dd, ^3J = 6.6 Hz ^3J = 2.7 Hz, 1 H, CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2, 15.3, 31.1, 41.3, 60.7, 61.1, 87.1, 108.7, 149.5, 157.2, 160.5.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{11}H_{18}N_5O_3S$: 300.1125; found: 300.1130.

7-Chloro-3-ethoxy-5-(methylsulfanyl)-2,3-dihydroimidazo[1,2-*c*]pyrimidine (5g)
Reaction time: 10 min. Yellowish oil; yield: 37 mg (50%); R_f = 0.15 (CH_2Cl_2–acetone, 9:1).

^1H NMR (300 MHz, $CDCl_3$): δ = 1.24 (t, *J* = 6.9 Hz, 3 H, CH_3), 2.59 (s, 3 H, SCH_3), 3.42 (dq, ^2J = 9.0 Hz, ^3J = 6.9 Hz, 1 H, CH_AH$_B$CH$_3$), 3.53 (dq, ^2J = 9.0 Hz, ^3J = 6.9 Hz, 1 H, CH$_A$H$_B$CH$_3$), 3.85 (dd, ^2J = 16.5 Hz, ^3J = 3.0 Hz, 1 H, NCH_AH$_B$CH), 3.94 (dd, ^2J = 16.5 Hz, ^3J = 7.2 Hz, 1 H, NCH$_A$H$_B$CH), 5.64 (dd, ^3J = 7.2 Hz ^3J = 3.0 Hz, 1 H, CH), 6.14 (s, 1 H, Ar-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 15.3, 59.3, 60.9, 86.9, 103.3, 153.1, 154.6, 161.0.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_9H_{13}ClN_3OS$: 246.0462; found: 246.0472.

3-Ethoxy-7-methoxy-5-(methylsulfanyl)-2,3-dihydroimidazo[1,2-*c*]pyrimidine (5h)
Reaction time: 1 h. Yellowish oil; yield: 32 mg (45%); R_f = 0.1 (MeOH).

^1H NMR (300 MHz, $CDCl_3$): δ = 1.22 (t, *J* = 6.9 Hz, 3 H, CH_3), 2.56 (s, 3 H, SCH_3), 3.39 (dq, ^2J = 9.0 Hz, ^3J = 6.9 Hz, 1 H, CH_AH$_B$CH$_3$), 3.52 (dq, ^2J = 9.0 Hz, ^3J = 6.9 Hz, 1 H, CH$_A$H$_B$CH$_3$), 3.78–3.87 (m, 4 H, NCH_AH$_B$CH and OCH$_3$), 3.92 (dd, ^2J = 16.2 Hz, ^3J = 7.2 Hz, 1 H, NCH$_A$H$_B$CH), 5.31 (s, 1 H, Ar-H), 5.63 (dd, ^3J = 7.2 Hz ^3J = 2.4 Hz, 1 H, CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.5, 15.2, 55.0, 59.0, 60.1, 79.2, 86.5, 157.1, 160.2, 166.3.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{10}H_{16}N_3O_2S$: 242.0958; found: 242.0967.

3-Ethoxy-7-methyl-5-(methylsulfanyl)-2,7-dihydro-3*H*-imidazo[1,2-*c*]pyrazolo[4,3-*e*]pyrimidine (5j)
Reaction time: 2 h. Yellowish solid; yield: 65 mg (82%); mp 123.5–125 °C; R_f = 0.15 (CH_2Cl_2–acetone, 2:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.23 (t, *J* = 6.9 Hz, 3 H, CH_3), 2.65 (s, 3 H, SCH_3), 3.39 (dq, ^2J = 9.0 Hz, ^3J = 6.9 Hz, 1 H, CH_AH$_B$CH$_3$), 3.54 (dq, ^2J = 9.0 Hz, ^3J = 6.9 Hz, 1 H, CH$_A$H$_B$CH$_3$), 3.90–3.99 (m, 4 H, NCH_AH$_B$CH and NCH_3), 4.04 (dd, ^2J = 16.2 Hz, ^3J = 6.9 Hz, 1 H, NCH$_A$H$_B$CH), 5.72 (dd, ^3J = 2.7 Hz ^3J = 6.9 Hz, 1 H, CH), 7.87 (s, 1 H, Ar-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 15.4, 34.3, 59.6, 60.4, 86.5, 98.5, 134.1, 150.0, 150.3, 158.3.

Anal. Calcd for $C_{11}H_{15}N_5OS$: C, 49.79; H, 5.70. Found: C, 49.93; H, 5.68.

3-Ethoxy-7-methyl-5-(methylsulfanyl)-2,7-dihydro-3*H*-imidazo[1,2-*c*]pyrazolo[4,3-*e*]pyrimidin-9-amine (5k)
Reaction time: 2 h. Yellowish solid; yield: 75 mg (89%); mp 104–106 °C; R_f = 0.1 (acetone).

IR (KBr): 3402, 3308, 3302 (NH_2) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.23 (t, *J* = 6.9 Hz, 3 H, CH_3), 2.62 (s, 3 H, SCH_3), 3.39 (dq, ^2J = 9.0 Hz, ^3J = 6.9 Hz, 1 H, CH_AH$_B$CH$_3$), 3.53 (dq, ^2J = 9.0 Hz, ^3J = 6.9 Hz, 1 H, CH$_A$H$_B$CH$_3$), 3.72 (s, 3 H, NCH_3), 3.73 (dq, ^2J = 15.9 Hz, ^3J = 2.1 Hz, 1 H, NCH_AH$_B$CH), 3.89 (dd, ^2J = 15.9 Hz, ^3J = 6.9 Hz, 1 H, NCH$_A$H$_B$CH), 5.06 (s, 2 H, NH_2), 5.65 (dd, ^3J = 6.9 Hz ^3J = 2.1 Hz, 1 H, CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7, 15.1, 33.2, 59.1, 60.0, 85.8, 86.0, 149.3, 149.5, 150.6, 158.0.

Anal. Calcd for $C_{11}H_{16}N_6OS$: C, 47.13; H, 5.75. Found: C, 47.28; H, 5.72.

3-Ethoxy-2,3-dihydroimidazo[1,2-*c*]pyrimidin-1-ium Tetrafluoroborates 6a–c and 6e–i; General Procedure
BF_3·OEt_2 (95 μL, 0.75 mmol) was added to a soln of the appropriate *N*-(2,2-diethoxyethyl)pyrimidin-4-amine **2a–i** (0.30 mmol) in CH_2Cl_2 (5 mL), and the mixture was stirred at r.t. for 10 min to 2 h. The solvent was evaporated to give an oily residue that solidified on shaking with Et_2O (15 mL) to give a product that was collected by filtration.

7-Chloro-8-cyano-3-ethoxy-5-(methylsulfanyl)-2,3-dihydroimidazo[1,2-*c*]pyrimidin-1-ium Tetrafluoroborate (6a)
Reaction time: 10 min. Colorless solid; yield: 101 mg (94%); mp 156 °C (dec.).

IR (KBr): 3168 (NH), 2233 (CN) cm^{-1}.

^{1}H NMR (300 MHz, CD_3CN): δ = 1.25 (t, *J* = 6.9 Hz, 3 H, CH_3), 2.80 (s, 3 H, SCH_3), 3.70 (dq, ^2J = 9.0 Hz, ^3J = 6.9 Hz, 1 H, CH_AH$_B$CH$_3$), 3.84 (dq, ^2J = 9.0 Hz, ^3J = 6.9 Hz, 1 H, CH$_A$H$_B$CH$_3$), 4.10 (dd, ^2J = 13.8 Hz, ^3J = 3.0 Hz, 1 H, NCH_AH$_B$CH), 4.23 (dd, ^2J = 13.8 Hz, ^3J = 7.8 Hz, 1 H, NCH$_A$H$_B$CH), 6.23 (dd, ^3J = 7.8 Hz ^3J = 3.0 Hz, 1 H, CH), 9.21 (br s, 1 H, NH).

^{13}C NMR (75 MHz, CD_3CN): δ = 14.2, 14.7, 50.0, 64.6, 87.2, 89.6, 109.9, 156.5, 164.7, 168.8.

HRMS (ESI): *m/z* [M$^+$] calcd for $C_{10}H_{12}ClN_4OS$: 271.0415; found: 271.0424.

8-Cyano-7-(dimethylamino)-3-ethoxy-5-(methylsulfanyl)-2,3-dihydroimidazo[1,2-*c*]pyrimidin-1-ium Tetrafluoroborate (6b)
Reaction time: 2 h. Yellowish solid; yield: 107 mg (97%); mp 170 °C (dec.).

IR (KBr): 3252 (NH), 2212 (CN) cm^{-1}.

^{1}H NMR (300 MHz, CD_3CN): δ = 1.26 (t, *J* = 6.9 Hz, 3 H, CH_3), 2.71 (s, 3 H, SCH_3), 3.43 (s, 3 H, NCH_3), 3.56 (s, 3 H, NCH_3), 3.66 (dq, ^2J = 9.0 Hz, ^3J = 6.9 Hz, 1 H, CH_AH$_B$CH$_3$), 3.79 (dq, ^2J = 9.0 Hz, ^3J = 6.9 Hz, 1 H, CH$_A$H$_B$CH$_3$), 3.92 (dd, ^2J = 12.6 Hz, ^3J = 2.4 Hz, 1 H, NCH_AH$_B$CH), 4.08 (dd, ^2J = 12.6 Hz, ^3J = 7.2 Hz, 1 H, NCH$_A$H$_B$CH), 6.02 (dd, ^3J = 7.2 Hz ^3J = 2.4 Hz, 1 H, CH), 7.90 (br s, 1 H, NH).

^{13}C NMR (75 MHz, CD_3CN): δ = 14.1, 14.5, 40.7, 49.8, 62.5, 63.8, 88.0, 114.2, 157.8, 159.2, 162.7.

HRMS (ESI): *m/z* [M$^+$] calcd for $C_{12}H_{18}N_5OS$: 280.1227; found: 280.1244.

8-Cyano-3-ethoxy-7-methoxy-5-(methylsulfanyl)-2,3-dihydroimidazo[1,2-*c*]pyrimidin-1-ium Tetrafluoroborate (6c)
Reaction time: 90 min. Colorless solid; yield: 92 mg (87%); mp 156 °C (dec.).

IR (KBr): 3276 (NH), 2233 (CN) cm^{-1}.

^{1}H NMR (300 MHz, CD_3CN): δ = 1.27 (t, *J* = 6.9 Hz, 3 H, CH_3), 2.84 (s, 3 H, SCH_3), 3.69 (dq, ^2J = 9.0 Hz, ^3J = 6.9 Hz, 1 H, CH_AH$_B$CH$_3$), 3.83 (dq, ^2J = 9.0 Hz, ^3J = 6.9 Hz, 1 H, CH$_A$H$_B$CH$_3$), 4.03 (dd, ^2J = 12.9 Hz, ^3J = 2.7 Hz, 1 H, NCH_AH$_B$CH), 4.16 (dd, ^2J = 12.9 Hz, ^3J = 7.2 Hz, 1 H, NCH$_A$H$_B$CH), 4.29 (s, 3 H, OCH_3), 6.00 (dd, ^3J = 7.2 Hz ^3J = 2.7 Hz, 1 H, CH), 8.59 (br s, 1 H, NH).

^{13}C NMR (75 MHz, CD_3CN): δ = 14.4, 14.7, 50.0, 52.6, 58.2, 64.2, 88.9, 110.3, 158.2, 169.6, 170.2.

HRMS (ESI): *m/z* [M$^+$] calcd for $C_{11}H_{15}N_4O_2S$: 267.0910; found: 267.0924.

3-Ethoxy-7-methoxy-5-(methylsulfanyl)-8-nitro-2,3-dihydroimidazo[1,2-*c*]pyrimidin-1-ium Tetrafluoroborate (6e)
Reaction time: 1 h. Yellowish solid; yield: 111 mg (96%); mp 170 °C (dec.).

IR (KBr): 3327 (NH) cm^{-1}.

^{1}H NMR (300 MHz, CD_3CN): δ = 1.28 (t, *J* = 6.9 Hz, 3 H, CH_3), 2.87 (s, 3 H, SCH_3), 3.73 (dq, ^2J = 9.0 Hz, ^3J = 6.9 Hz, 1 H, CH_AH$_B$CH$_3$), 3.86 (dq, ^2J = 9.0 Hz, ^3J = 6.9 Hz, 1 H, CH$_A$H$_B$CH$_3$), 4.14 (dd, ^2J = 12.6 Hz, ^3J = 2.7 Hz, 1 H, NCH_AH$_B$CH), 4.29 (dd, ^2J = 12.6 Hz, ^3J = 7.2 Hz, 1 H, NCH$_A$H$_B$CH), 4.37 (s, 3 H, OCH_3), 6.02 (dd, ^3J = 7.2 Hz ^3J = 2.7 Hz, 1 H, CH), 9.29 (br s, 1 H, NH).

^{13}C NMR (75 MHz, CD_3CN): δ = 14.4, 14.9, 50.9, 58.7, 64.3, 84.4, 88.9, 153.5, 163.5, 169.2.

HRMS (ESI): *m/z* [M$^+$] calcd for $C_{10}H_{15}N_4O_4S$: 287.0809; found: 287.0817.

7-(Dimethylamino)-3-ethoxy-5-(methylsulfanyl)-8-nitro-2,3-dihydroimidazo[1,2-*c*]pyrimidin-1-ium Tetrafluoroborate (6f)
Reaction time: 2 h. Yellow solid; yield: 109 mg (96%); mp 138 °C (dec.).

IR (KBr): 3341, 3220 (NH) cm^{-1}.

^{1}H NMR (300 MHz, CD_3CN): δ = 1.27 (t, *J* = 6.9 Hz, 3 H, CH_3), 2.75 (s, 3 H, SCH_3), 3.11 (s, 3 H, NCH_3), 3.53 (s, 3 H, NCH_3), 3.68–3.90 (m, 2 H, CH_2CH$_3$), 4.05 (dd, ^2J = 13.2 Hz, ^3J = 2.1 Hz, 1 H, NCH_AH$_B$CH), 4.19 (dd, ^2J = 13.2 Hz, ^3J = 7.2 Hz, 1 H, NCH$_A$H$_B$CH), 6.02 (dd, ^3J = 7.2 Hz ^3J = 2.1 Hz, 1 H, CH), 8.93 (br s, 1 H, NH).

^{13}C NMR (75 MHz, CD_3CN): δ = 14.47, 14.52, 40.6, 43.2, 51.2, 64.3, 87.8, 108.1, 153.5, 155.1, 161.7.

HRMS (ESI): *m/z* [M$^+$] calcd for $C_{11}H_{18}N_5O_3S$: 300.1125; found: 300.1133.

7-Chloro-3-ethoxy-5-(methylsulfanyl)-2,3-dihydroimidazo[1,2-*c*]pyrimidin-1-ium Tetrafluoroborate (6g)
Reaction time: 10 min. Colorless solid; yield: 96 mg (96%); mp 130 °C (dec.).

IR (KBr): 3253 (NH) cm^{-1}.

^{1}H NMR (300 MHz, CD_3CN): δ = 1.27 (t, *J* = 6.9 Hz, 3 H, CH_3), 2.75 (s, 3 H, SCH_3), 3.67 (dq, ^2J = 9.0 Hz, ^3J = 6.9 Hz, 1 H,

CH_AH$_B$CH$_3$), 3.83 (dq, ^2J = 9.0 Hz, ^3J = 6.9 Hz, 1 H, CH$_A$$H_BCH_3$), 4.00 (dd, ^2J = 10.2 Hz, ^3J = 1.5 Hz, 1 H, NCH_AH$_B$CH), 4.12 (dd, ^2J = 10.2 Hz, ^3J = 7.5 Hz, 1 H, NCH$_A$$H_B$CH), 6.13 (dd, ^3J = 7.5 Hz ^3J = 1.5 Hz, 1 H, CH), 6.89 (s, 1 H, Ar-H), 8.23 (br s, 1 H, NH).

^{13}C NMR (75 MHz, CD$_3$CN): δ = 14.2, 14.4, 49.8, 64.2, 88.7, 99.2, 157.9, 161.8, 166.8.

HRMS (ESI): *m/z* [M$^+$] calcd for $C_9H_{13}ClN_3OS$: 246.0462; found: 246.0472.

3-Ethoxy-7-methoxy-5-(methylsulfanyl)-2,3-dihydroimidazo[1,2-*c*]pyrimidin-1-ium Tetrafluoroborate (6h)

Reaction time: 1 h. Colorless solid; yield: 73 mg (74%); mp 120 °C (dec.).

IR (KBr): 3359 (NH) cm^{-1}.

^{1}H NMR (300 MHz, CD$_3$CN): δ = 1.26 (t, *J* = 6.9 Hz, 3 H, CH$_3$), 2.76 (s, 3 H, SCH$_3$), 3.65 (dq, ^2J = 9.0 Hz, ^3J = 6.9 Hz, 1 H, CH_AH$_B$CH$_3$), 3.80 (dq, ^2J = 9.0 Hz, ^3J = 6.9 Hz, 1 H, CH$_A$$H_BCH_3$), 4.00 (dd, ^2J = 12.6 Hz, ^3J = 2.4 Hz, 1 H, NCH_AH$_B$CH), 4.02 (dd, ^2J = 12.6 Hz, ^3J = 7.2 Hz, 1 H, NCH$_A$$H_B$CH), 4.11 (s, 3 H, OCH$_3$), 6.01 (s, 1 H, Ar-H), 6.05 (dd, ^3J = 7.2 Hz ^3J = 2.4 Hz, 1 H, CH), 7.59 (br s, 1 H, NH).

^{13}C NMR (75 MHz, CD$_3$CN): δ = 14.0, 14.5, 49.5, 56.5, 63.7, 79.9, 87.8, 159.0, 164.8, 170.5.

HRMS (ESI): *m/z* [M$^+$] calcd for $C_{10}H_{16}N_3O_2S$: 242.0958; found: 242.0967.

7-(Dimethylamino)-3-ethoxy-5-(methylsulfanyl)-2,3-dihydroimidazo[1,2-*c*]pyrimidin-1-ium Tetrafluoroborate (6i)

Reaction time: 2 h; colorless solid; yield: 97 mg (95%); mp 135 °C (dec.).

IR (KBr): 3363 (NH) cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.17 (t, *J* = 6.9 Hz, 3 H, CH$_3$), 2.66 (s, 3 H, SCH$_3$), 3.08 (s, 3 H, NCH$_3$), 3.29 (s, 3 H, NCH$_3$), 3.53 (dq, ^2J = 9.0 Hz, ^3J = 6.9 Hz, 1 H, CH_AH$_B$CH$_3$), 3.68 (dq, ^2J = 9.0 Hz, ^3J = 6.9 Hz, 1 H, CH$_A$$H_BCH_3$), 3.80 (dd, ^2J = 12.0 Hz, ^3J = 1.8 Hz, 1 H, NCH_AH$_B$CH), 3.91 (dd, ^2J = 12.0 Hz, ^3J = 6.9 Hz, 1 H, NCH$_A$$H_B$CH), 5.55 (s, 1 H, Ar-H), 6.00 (dd, ^3J = 6.9 Hz ^3J = 1.8 Hz, 1 H, CH), 9.06 (br s, 1 H, NH).

^{13}C NMR (75 MHz, CD$_3$CN): δ = 14.2, 15.5, 38.4, 38.8, 49.1, 62.8, 73.0, 87.1, 156.4, 160.4, 160.8.

HRMS (ESI): *m/z* [M$^+$] calcd for $C_{11}H_{19}N_4OS$: 255.1274; found: 255.1286.

4-Chloro-6-methoxy-2-(methylsulfanyl)-5-nitropyrimidine (9)

Na_2CO_3 (0.49 g, 4.62 mmol) was added to a soln of pyrimidine **7**[17] (1.0 g, 4.16 mmol) in MeOH (30 mL), and the mixture was stirred at r.t. for 6 h. H_2O (150 mL) was added and the resulting precipitate was collected by filtration, dried, and crystallized (hexane) to give a colorless solid; yield: 0.63 g (64%); mp 78–79 °C (Lit.[19] 77.5–79.5 °C).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 2.60 (s, 3 H, SCH$_3$), 4.13 (s, 3 H, OCH$_3$).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 14.8, 56.2, 128.8, 151.4, 160.9, 173.8.

Anal. Calcd for $C_6H_6ClN_3O_3S$: C, 30.58; H, 2.57. Found: C, 30.75; H, 2.54.

4-Chloro-6-[(2,2-diethoxyethyl)amino]-2-(methylsulfanyl)pyrimidine-5-carbaldehyde (10)

2,2-Diethoxyethylamine (3.6 mL, 24.7 mmol) was added to a suspension of 4,6-dichloro-2-(methylsulfanyl)pyrimidine-5-carbaldehyde[16] (5.0 g, 22.4 mmol) in *i*-PrOH (100 mL), and the mixture was stirred until all the crystals had dissolved. Et$_3$N (3.4 mL 24.3 mmol) was then added. After 10 min, the solvent was evaporated under reduced pressure, and the product was extracted with CH$_2$Cl$_2$ (50 mL). The soln was washed with H_2O (2 × 50 mL), dried (Na_2SO_4), and concentrated. The crude product was crystallized from hexane at –15 °C to give a yellowish solid; yield: 5.34 g (75%); mp 104–106 °C.

IR (KBr): 3268 (NH), 1654 (C=O) cm^{-1}.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.28 (t, *J* = 6.9 Hz, 6 H, 2 × CH$_3$), 2.56 (s, 3 H, SCH$_3$), 3.61 (dq, ^2J = 9.3 Hz, ^3J = 6.9 Hz, 2 H, 2 × CH_AH$_B$CH$_3$), 3.72–3.84 (m, 4 H, NCH$_2$ and 2 × CH$_A$$H_BCH_3$), 4.67 (t, *J* = 5.4 Hz, 1 H, OCH), 9.42 (br s, 1 H, NH), 10.27 (s, 1 H, CHO).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 14.7, 15.6, 43.6, 63.1, 100.5, 105.0, 160.4, 164.6, 177.0, 190.5.

Anal. Calcd for $C_{12}H_{18}ClN_3O_3S$: C, 45.07; H, 5.67. Found: C, 45.29; H, 5.67.

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