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Functionalization of Position 7 of Pyrazolo[1,5-*a*]pyrazines

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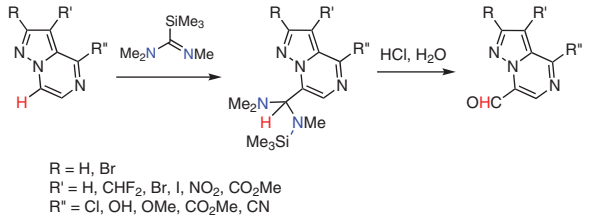

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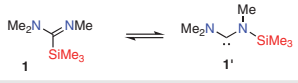
Abstract We report a straightforward formylation at position 7 of pyrazolo[1,5-*a*]pyrazine derivatives featuring substituents at the 2,3,4 positions. *N*,*N*,*N*′,1,1,1-Hexamethylsilanecarboximidamide exists in equilibrium with its carbene form due to 1,2-migration of the silyl group. The ensuing carbene can be inserted into the most acidic C–H group of the pyrazolo[1,5-*a*]pyrazines. The most acidic calculated pK_a (DMSO) C–H group is at position 7 and does not depend significantly on the substituents. The reactions proceed in high yields affording aminals that can be hydrolyzed to the corresponding aldehydes. Methanolysis of the aminals affords the corresponding methylimines. The constitution of the aminals was unambiguously proved by X-ray crystal structure analysis of a set of derivatives. The method is simple, often does not require even solvents, and can be extended to other heterocyclic compounds.

Key words pyrazolo[1,5-*a*]pyrazine, diaminomethylation, aldehyde, carbene, C–H insertion

Pyrazolo[1,5-*a*]pyrazines are representatives of an important class of heterocyclic systems with powerful synthetic and biological potential.[1] In recent years, systematic studies have identified many of its derivatives as inhibitors of several types of kinases,[2–5] dopamine receptor agonists,[6] antagonists of vasopressin V1b,[7] fibrinogen,[8] chemokine CXCR7,[9] and orexin[10] receptors. Modern approaches to new pharmacologically promising compounds based on the pyrazolo[1,5-*a*]pyrazine scaffold are limited to modification of the pyrazine ring, in particular at positions 4 and 5 of the heterocyclic core.[11–14] To our knowledge, there have been no previous attempts at functionalization at position 7 of the pyrazolo[1,5-*a*]pyrazine ring, which would contribute to a significant expansion of the chemical space of compounds for biomedical research. We have recently shown that *N*,*N*,*N*′,1,1,1-hexamethylsilane-carboximidamide **1** exists in equilibrium with its carbene form **1′** (Scheme 1). Although the carbene form was not detected even spectroscopically, compound **1** behaves like a highly active nucleophilic carbene. Thus, we have shown that it inserts into sp-, sp^2-, and sp^3 C–H bonds, affording the corresponding aminals.[15] We have also elucidated the mechanism of the insertion reaction. On a set of benzene and pyridine derivatives, it was shown that the first step of the reaction is deprotonation of the most acidic C–H hydrogen, resulting in the formation of a tight ion pair of a formamidinium cation and a substrate anion that combine to form the final insertion product. We have extended the reaction to thiophene derivatives and demonstrated that this very simple approach can be used to prepare aldehydes of different types of heterocycles. Additionally, we have evaluated an approximate pK_a range of a C–H group that could potentially react with silylformamidine **1**. Silylformamidine is not commercially available at present; however, within laboratory settings, it can be synthesized in two steps on a 100-g scale, starting from trimethylformamidine and trimethylsilyl triflate, followed by deprotonation using hexamethylsilazanide lithium. It exhibits considerable stability, facilitating long-term storage. Furthermore, it demonstrates versatility in its tolerance towards numerous functional groups. Notably, it exhibits vigorous reactivity towards highly acidic functional groups containing a heteroatom–hydrogen moiety.[15]



Scheme 1 *N*,*N*,*N*′,1,1,1-Hexamethylsilane-carboximidamide in equilibrium with the carbene form

Determination of C–H acidity of aromatic and heteroaromatic compounds is not an easy task to perform, but recently a program (https://pka.allchemy.net) was developed and offered free that can promptly evaluate the pK_a of any organic compound with accuracy of 2 units. In this way, one can relatively easily estimate the most acidic position in the molecule and predict whether it will react with silylformamidine.

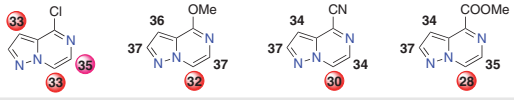
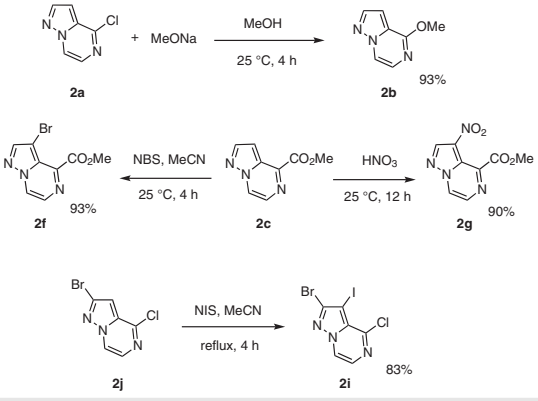


Figure 1 pK_a values calculated for compounds **2a–d** in DMSO

As the introduction of a substituent can alter the pK_a of a molecule markedly, we decided to study whether pyrazolo[1,5-*a*]pyrazine derivatives will be suitable substrates for the reaction with silylformamidine. We calculated the pK_a values of all our available substrates using the freely available software at https://pka.allchemy.net in DMSO, CH_3CN and THF;[16] these data are given in Table S1. For further use, we considered pK_a values calculated in DMSO. Thus, for 4-substituted derivatives **2a–d** the calculations show that the most acidic C–H group is located at the 7-position. It is also clear that substituents affect pK_a, with electron-donating substituents increasing pK_a and electron-accepting substituents decreasing it (Figure 1).

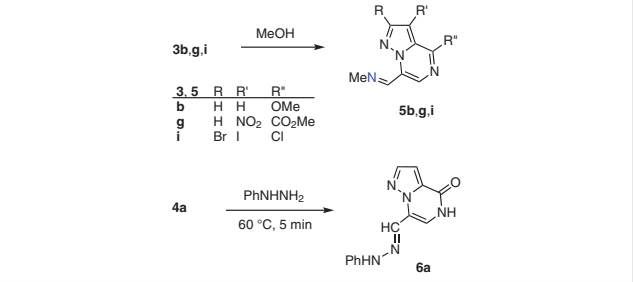
Synthesis of the Starting Compounds

Compounds **2a**, **2c**, **2d**, and **2j** were prepared according to a reported procedure.[17] Compound **2b** was synthesized by nucleophilic substitution of 4-chloropyrazolo[1,5-*a*]pyrazine **2a** with sodium methoxide. Compounds **2f** and **2g** were obtained starting from methyl carboxylate **2c** by bromination with *N*-bromosuccinimide (NBS) and nitration, respectively. Polyhalogenated derivative **2i** was produced by iodination of 2-bromo-4-chloropyrazolo[1,5-*a*]pyrazine (**2j**) (Scheme 2). Compounds **2e** and **2h** were purchased (Enamine Ltd.) and used as received.



Scheme 2 Synthesis of the starting compounds **2**

We started our investigation by mixing 4-chloropyrazolo[1,5-*a*]pyrazine **2a** with silylformamidine **1** (1.5 equiv) without solvent and, after stirring at room temperature for 4 days, the reaction proceeded cleanly to afford the target product in over 90% yield by insertion of the carbene into the C–H bond (Table 1, entry 1). We then found that it is possible to carry out the reaction at elevated temperature 70–90 °C for a shorter time (10 h). On going to 4-methoxypyrazolo[1,5-*a*]pyrazine **2b**, it was found that the reaction proceeded only on heating the reaction mixture. Heating the reagents for 2 days at 70 °C afforded aminal **3c** in 58% yield (entry 3). Electron-accepting substituents increased the rate of the reaction. Thus, 4-methoxycarbonyl derivative **2c** reacted with silylformamidine **1** at 90 °C for 30 min giving aminal **3c** in 71% yield (entry 4). Additionally, 4-cyano derivative **2d** reacted at room temperature in 50% yield (entry 5). Thus, it is clear that electron-accepting substituents promote the insertion reaction. 4-Substituted pyrazolo[1,5-*a*]pyrazine derivatives are readily reacted at the 3-position via electrophilic substitution reaction so that these compounds are easily accessible. Thus, we further studied 3-substituted methyl pyrazolo[1,5-*a*]pyrazine-4-carboxylates **2e–h**. Additional electron-withdrawing substituents at the heterocyclic core further facilitated the insertion reaction (Scheme 3).



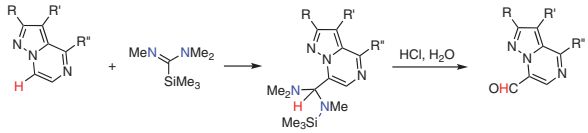
Scheme 3 Synthesis of imines **5** and hydrazone **6a**

These compounds reacted either upon short-term heating or after a longer period at room temperature. We failed to isolate aminal **3f** in analytically pure form, so this was used for further transformation without any purification. Polyhalogen substituted compound **3i** reacted readily and was isolated in high yield (entry 10).

As the aminals are typically produced from aldehydes, we attempted to hydrolyse them to give the corresponding aldehydes. Hydrolysis of aminal **3a** was accompanied by nucleophilic substitution of chloride with water to afford aldehyde **4a**.

Hydrolysis of aminals **3** proceeded quite well, affording the corresponding aldehydes in high yield (Table 1). Hydrolysis of aminals **3b**, **3d**, and **3i** afforded intractable mixtures from which we failed to isolate any individual compounds. Likely, these compounds are too active and undergo side reactions during hydrolysis. Aldehydes **4c** and **4e** are poorly

Table 1 The Reaction of Pyrazolo[1,5-*a*]pyrazine Derivatives **2** with Silylformamidine **1**



2a–h **1** **3a–h** **4a–e**

Entry	Compd	R	R′	R′′	Reaction conditions for **3**	Yield of aminal **3** (%)	Reaction conditions for **4**	Yield of aldehyde **4** (%)
1	**2a**	H	H	Cl	**1** (1.5 equiv), r.t., 4 days	93	aminal (3 mmol), aq. HCl (15%; 2 mL), 60 °C, 10 min	93
2	**4a**	H	H	OH				
3	**2b**	H	H	OMe	**1** (2 equiv), 70 °C, 2 days	58		–
4	**2c**	H	H	CO_2Me	**1** (2 equiv), 90 °C, 30 min	71	as for **3a**	83
5	**2d**	H	H	CN	**1** (2 equiv), r.t., 20 h	50		–
6	**2e**	H	CHF_2	CO_2Me	**1** (3 equiv), 60 °C, 15 min	88	as for **3a**	87
7	**2f**	H	Br	CO_2Me	**1** (3 equiv), r.t., 20 h	90	aminal (3 mmol), aq. HBr (20%; 2 mL), 60 °C, 10 min	52
8	**2g**	H	NO_2	CO_2Me	**1** (3 equiv), benzene, r.t., 30 min then 50 °C, 10 min	77	as for **3a**	80
9	**2h**	H	CO_2Me	CO_2Me	**1** (3 equiv), r.t., 24 h	71	as for **3a**	51
10	**2i**	Br	I	Cl	**1** (3 equiv), 80 °C, 5 min	82		–

soluble in $CDCl_3$ so NMR spectra were recorded in DMSO-d_6. Both compounds are present in two forms: the aldehyde itself and its hydrated form. Addition of water to DMSO solution almost completely shifted the equilibrium to the hydrated form (see the Supporting Information). NMR spectra of aldehydes **4f**, **4g**, and **4h** recorded in $CDCl_3$ exhibited exclusively peaks from the aldehyde form. Previously we showed that aminals of type **3** undergo methanolysis to afford the corresponding methylimines. Thus, we carried out methanolysis of aminals **3b** and **3i** (compounds with which we failed to prepare aldehydes). Additionally, methanolysis was performed for aminal **3g**, which gave the corresponding aldehyde. In all cases, methanolysis afforded the corresponding methylimines **5b**, **5g**, and **5i** in good yield.

In order to establish unambiguously the position at which the insertion occurred, the molecular structure of compounds **3f** and **3g** were determined by single-crystal X-ray diffraction. As we failed to grow crystals for aminal **3a** or aldehyde **4a**, we prepared its phenylhydrazone derivative **6a**, which gave good-quality single crystals. The X-ray studies confirmed that the insertion occurred at the 7-position in all cases (Figure 2). As depicted in Figure 1, the introduction of substituents at the heterocyclic core significantly influences the pK_a of C–H groups. In compound **2a**, calculations indicate an identical pK_a value of 33 for positions 3 and 7. However, in our experiments, we observed solely the insertion at position 7, with no detectable traces of other regioisomers. Compound **6a** exists as an NH tautomer in the crystal phase. This fact was confirmed by the determination of the hydrogen atom at the N1 atom from electron density difference maps and the length of the C1–O1 bond (1.240(4) Å), which is close to the mean value of the C=O bond (1.210 Å) (Figure 2). Some elongation of the carbonyl bond is due to its participation in the N5–H···O1′ intermolecular hydrogen bond (symmetry operation is 0.5+*x*, 0.5+*y*, 0.5–*z*; H···O distance is 2.04 Å, N–H···O angle is 165°).

In conclusion, we have devised a straightforward method to formylate substituted pyrazolo[1,5-*a*]pyrazines at the 7-position. Considering the ready availability of the starting pyrazolo[1,5-*a*]pyrazines, the high yields of the reaction, and tolerance to various substituents, we are convinced that it is a convenient and short approach to previously unknown compounds.

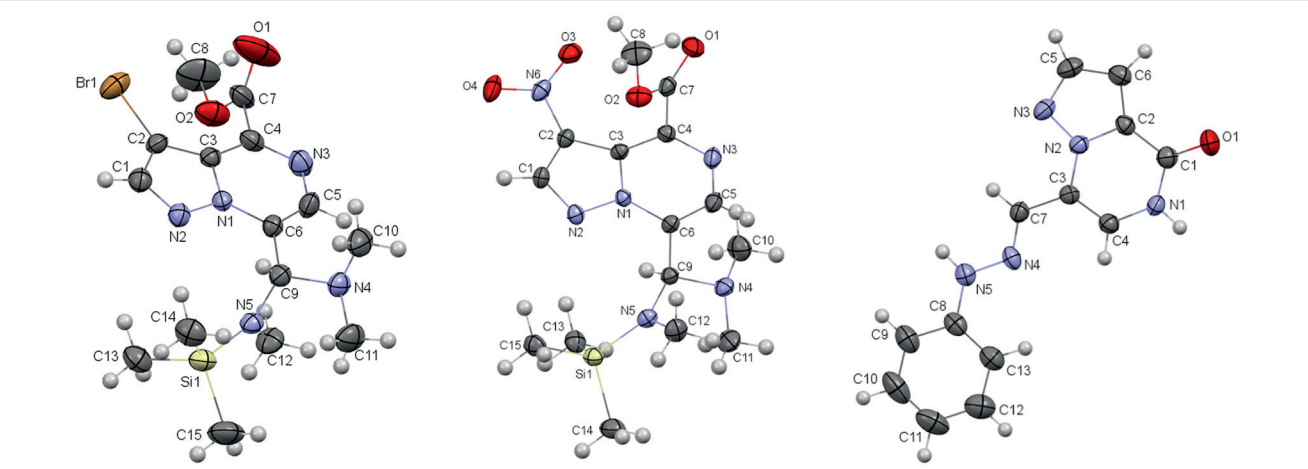


Figure 2 Molecular structure of **3f** (left), **3g** (middle), and **6a** (right) according to X-ray diffraction data. Thermal ellipsoids are shown at 50% probability level

All solvents were purified according to the standard procedures.

^{1}H and ^{13}C NMR spectra were recorded with a Bruker 170 Avance 500 spectrometer (500 MHz for ^{1}H NMR, 126 MHz for ^{13}C NMR) and a Varian Unity Plus 400 spectrometer (400 MHz for ^{1}H NMR, 101 MHz for ^{13}C NMR). NMR chemical shifts are reported in ppm (δ scale) and are referenced using residual NMR solvent peaks at δ = 7.26 and 77.16 ppm for ^{1}H and ^{13}C in $CDCl_3$, and at δ = 7.16 (^{1}H), 128.0 (^{13}C) in C_6D_6, respectively. Elemental analyses were performed at the Laboratory of Organic Analysis. Mass spectra were recorded with an Agilent 1100 LCMSD SL instrument (chemical ionization (CI)) and Agilent 5890 Series II 5972 MS instrument (electron impact ionization (EI)). High-resolution mass spectra (HRMS) were obtained with an Agilent 1260 Infinity UHPLC instrument coupled with an Agilent 6224 Accurate Mass TOF mass spectrometer.

4-Methoxypyrazolo[1,5-*a*]pyrazine (2b)

4-Chloropyrazolo[1,5-*a*]pyrazine **2a** (1.54 g, 0.01 mol) was dissolved in a sodium methylate solution prepared by dissolving sodium (0.46 g, 20 mmol) in anhydrous MeOH (20 mL), then the reaction mixture was stirred at r.t. for 4 h. An aqueous 20% solution of ammonium chloride was added and MeOH was evaporated under reduced pressure. The aqueous residue was extracted with dichloromethane (2 × 10 mL). All volatiles were then evaporated and the residue was sublimated (0.1 Torr, oil bath temperature 90 °C) to afford **2b**.

Yield: 93% (1.39 g); white solid; mp 85–86 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.0 (d, *J* = 5 Hz, 1 H), 7.9 (d, *J* = 2 Hz, 1 H), 7.32 (d, *J* = 5 Hz, 1 H), 6.75 (s, 1 H), 4.08 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.0, 140.9, 128.5, 125.7, 117.1, 98.2, 53.8.

Anal. Calcd for $C_7H_7N_3O$: C, 56.37; H, 4.73; N, 28.17. Found: C, 56.54; H, 5.15; N, 27.96.

Methyl 3-Bromopyrazolo[1,5-*a*]pyrazine-4-carboxylate (2f)

To a solution of *N*-bromosuccinimide (NBS) (1.06 g, 5.9 mmol) in anhydrous MeCN (50 mL) at r.t., methyl pyrazolo[1,5-*a*]pyrazine-4-carboxylate **2c** (1 g, 5.6 mmol) was added. The reaction mixture was stirred for 3 h then the solvent was evaporated. Water (50 mL) was added to the solid residue, and the resulting mixture was filtered off, washed successively with water (25 mL) and methyl *tert*-butyl ether (20 mL), and dried in air.

Yield: 93% (1.34 g); yellow powder; mp 88 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.01 (d, *J* =4.4 Hz, 1 H, H-7), 8.45 (s, 1 H, H-2), 8.04 (d, *J* =4.4 Hz, 1 H, H-6), 4.01 (s, 3 H, OCH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 164.0, 144.8, 144.6, 130.1, 129.2, 125.2, 86.2, 53.6.

MS: *m*/*z* (%) = 257 (100) $[M + H]^+$.

IR: 1680, 1725 (C=O), 3346 (NH) cm^{-1}.

Anal. Calcd for $C_8H_6BrN_3O_2$: C, 37.53; H, 2.36; N, 16.41. Found: C, 37.80; H, 2.25; N, 16.18.

Methyl 3-Nitropyrazolo[1,5-*a*]pyrazine-4-carboxylate (2g)

To a solution of methyl pyrazolo[1,5-*a*]pyrazine-4-carboxylate **2c** (1 g, 5.6 mmol) in H_2SO_4 (10 mL) at 0 °C, HNO_3 (2 mL) was added dropwise. The reaction mixture was stirred overnight at r.t. then poured onto ice and the resulting mixture was filtered off, washed with cold water (10 mL), and dried in vacuo.

Yield: 90% (1.12 g); yellow powder; mp 185 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.29 (d, *J* = 4.2 Hz, 1 H, H-7), 9.18 (s, 1 H, H-2), 8.45 (d, *J* = 4.2 Hz, 1 H, H-6), 3.97 (s, 3 H, OCH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 164.3, 145.2, 142.1, 133.1, 126.8, 126.3, 125.2, 53.7.

MS: *m*/*z* (%) = 223 (100) $[M + H]^+$.

IR: 1680, 1725 (C=O), 3346 (NH) cm^{-1}.

Anal. Calcd for $C_8H_6N_4O_4$: C, 43.25; H, 2.72; N, 25.22. Found: C, 43.12; H 2.69; N, 25.44.

2-Bromo-4-chloro-3-iodopyrazolo[1,5-*a*]pyrazine (2i)

To a solution of *N*-iodosuccinimide (1.02 g, 4.52 mmol) in anhydrous MeCN (50 mL) at r.t., 2-bromo-4-chloropyrazolo[1,5-*a*]pyrazine **2j** (1 g, 4.3 mmol) was added. The reaction mixture was heated at reflux for 4 h, the solvent was evaporated, water (50 mL) was added to the solid residue, and the resulting mixture was filtered off, washed with water (30 mL), Et_2O (20 mL), and dried in air.

Yield: 83% (1.28 g); white powder; mp 140 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.91 (d, *J* =4.8 Hz, 1 H, H-7), 7.81 (d, *J* = 4.8 Hz, 1 H, H-6).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 142.1, 140.2, 134.6, 128.8, 123.6, 60.9.

MS: *m*/*z* (%) = 359 (100) $[M + H]^+$.

IR: 1680, 1725 (C=O), 3346 (NH) cm^{-1}.

Anal. Calcd for $C_6H_2BrClIN_3$: C, 20.11; H, 0.56; N, 11.73. Found: C, 20.25; H, 0.44; N, 11.58.

Synthesis of Aminals 3; General Procedure

A 15 mL flask was charged with silylformamidine **1** (1 g, 6.3 mmol) and pyrazolo[1,5-*a*]pyrazine **2** (2 mmol). The mixture was stirred on a water bath (70–90 °C) until a homogeneous solution was formed. Excess silylformamidine **1** was distilled off (a water bath up to 90 °C; 0.1 Torr). The residue was dissolved in hexane (30 mL) under heating. It can be treated with activated carbon at r.t.. After cooling to r.t., the solution was filtered from impurities. The filtrate was evaporated to dryness, then the residue was dissolved in pentane (5 mL) and left to crystallize at –10 °C. The precipitated crystals were filtered, washed with cold pentane (25 mL), and dried.

1-(4-Chloropyrazolo[1,5-*a*]pyrazin-7-yl)-*N*,*N*,*N*′-trimethyl-*N*′-(trimethylsilyl)methanediamine (3a)

A mixture of silylformamidine **1** (1 g, 6.3 mmol) and 4-chloropyrazolo[1,5-*a*]pyrazine **2a** (3.07 g, 2 mmol) was stirred at r.t. for 4 days. Excess silylformamidine **1** was distilled off to give compound **3a**.

Yield: 93% (1.89 g); slightly yellow crystals; mp 60–62 °C.

^{1}H NMR (400 MHz, C_6D_6): δ = 7.97 (s, 1 H), 7.64 (s, 1 H), 6.49 (s, 1 H), 5.09 (s, 1 H), 2.02 (s, 9 H), 0.17 (s, 9 H).

^{13}C NMR (150 MHz, C_6D_6): δ = 142.3, 141.0, 134.8, 131.7, 126.8, 132.4, 99.6, 74.9, 41.6, 26.9, –0.6.

Anal. Calcd for $C_{13}H_{22}ClN_5Si$: C, 50.06; H, 7.11; N, 22.45. Found: C, 50.09; H, 6.87; N, 22.32.

1-(4-Methoxypyrazolo[1,5-*a*]pyrazin-7-yl)-*N*,*N*,*N*′-trimethyl-*N*-(trimethylsilyl)methanediamine (3b)

Yield: 58 % (1.2 g); white crystals; mp 62–63 °C; bp 122–125 °C / 0.1 Torr.

^{1}H NMR (400 MHz, C_6D_6): δ = 7.84 (s, 1 H), 7.73 (s, 1 H), 6.69 (s, 1 H), 5.19 (s, 1 H), 3.83 (s, 3 H), 2.19 (s, 3 H), 2.15 (s, 6 H), 0.24 (s, 9 H).

^{13}C NMR (125 MHz, C_6D_6): δ = 155.3, 139.5, 128.4, 126.5, 124.5, 97.7, 74.6, 52.6, 41.6, 26.6, –0.8.

Anal. Calcd for $C_{14}H_{25}N_5OSi$: C, 54.69; H, 8.20; N, 22.78. Found: C, 54.76; H, 8.31; N, 22.65.

Methyl 7-((Dimethylamino)(methyl(trimethylsilyl)amino)methyl)pyrazolo[1,5-*a*]pyrazine-4-carboxylate (3c)

A mixture of methyl carboxylate **2c** (1 g, 5.6 mmol) and silylformamidine **1** (1.7 g, 11 mmol) was heated at 90 °C for 30 min. Excess silylformamidine **1** was evaporated under a reduced pressure. The residue was recrystallized from hexane. The solution was left at –10 °C to afford aminal **3c**.

Yield: 71% (1.22 g); yellow crystals; mp 117–118 °C.

^{1}H NMR (400 MHz, C_6D_6): δ = 8.40 (s, 1 H), 7.83 (s, 1 H), 7.44 (s, 1 H), 5.22 (s, 1 H), 3.58 (s, 3 H), 2.06 (s, 3 H), 2.03 (s, 6 H), 0.17 (s, 9 H).

^{13}C NMR (150 MHz, C_6D_6): δ = 164.1, 152.7, 142.1, 140.5, 135.6, 135.1, 101.0, 75.1, 51.8, 41.5, 27.0, –0.6.

Anal. Calcd for $C_{15}H_{25}N_5O_2Si$: C, 53.70; H, 7.51; N, 20.88. Found: C, 53.63; H, 7.32; N, 21.10.

7-((Dimethylamino)(methyl(trimethylsilyl)amino)methyl)pyrazolo[1,5-*a*]pyrazine-4-carbonitrile (3d)

Nitrile **2d** (1 g, 7 mmol) and silylformamidine **1** (2.2 g, 14 mmol) were mixed and stirred at r.t. for 20 h. The reaction mixture turned dark brown. Excess silylformamidine was evaporated under a reduced pressure. The residue was treated with activated charcoal in pentane and recrystallized from pentane. The solution was left at –20 °C to afford aminal **3d**.

Yield: 50% (1.06 g); yellow crystals; mp 72–73 °C.

^{1}H NMR (400 MHz, C_6D_6): δ = 8.16 (s, 1 H), 7.55 (s, 1 H), 6.40 (s, 1 H), 5.06 (s, 1 H), 1.96 (s, 9 H), 0.14 (s, 9 H).

^{13}C NMR (150 MHz, C_6D_6): δ = 141.9, 136.1, 135.4, 127.9, 126.0, 114.6, 98.0, 74.5, 41.0, 26.6, –0.9.

Anal. Calcd for $C_{14}H_{22}N_6Si$: C, 55.60; H, 7.33; N, 27.79. Found: C, 55.78; H, 7.349; N, 27.68.

Methyl 3-(Difluoromethyl)-7-((dimethylamino)(methyl(trimeth-yl-silyl)amino)methyl)pyrazolo[1,5-*a*]pyrazine-4-carboxylate (3e)

A mixture of compound **2e** (1 g, 4.4 mmol) and silylformamidine **1** (2.1 g, 13.3 mmol) was heated at 60 °C for 15 min. After cooling to r.t., excess silylformamidine was removed under reduced pressure to afford aminal **3e**.

Yield: 88% (580 mg); viscous yellow oil.

^{1}H NMR (400 MHz, C_6D_6): δ = 8.38 (s, 1 H), 8.20 (s, 1 H), 7.67 (t, *J* = 57 Hz, 1 H), 5.11 (s, 1 H), 3.52 (s, 3 H), 1.99 (s, 9 H), 0.13 (s, 9 H).

Methyl 3-Bromo-7-((dimethylamino)(methyl(trimethylsilyl)amino)methyl)pyrazolo[1,5-*a*]pyrazine-4-carboxylate (3f)

A mixture of compound **2f** (1 g, 4 mmol) and silylformamidine **1** (1.9 g, 12 mmol) was stirred at r.t. for 20 h. After removal of excess silylformamidine under reduced pressure, the residue was recrystallized from pentane to afford aminal **3f**.

Yield: 90% (1.45 g); yellowish solid; mp 113–114 °C.

^{1}H NMR (400 MHz, C_6D_6): δ = 8.26 (s, 1 H), 7.64 (s, 1 H), 5.02 (s, 1 H), 3.61 (s, 3 H), 1.97 (s, 6 H), 1.94 (s, 3 H), 0.11 (s, 9 H).

^{13}C NMR (125 MHz, C_6D_6): δ = 163.5, 143.5, 142.4, 142.1, 133.7, 130.6, 86.1, 74.3, 51.7, 41.1, 26.6, –0.9.

Anal. Calcd for $C_{15}H_{24}BrN_5O_2Si$: C, 43.48; H, 5.84; N, 16.90. Found: C, 43.73; H, 5.56; N, 17.12.

Methyl 7-((Dimethylamino)(methyl(trimethylsilyl)amino)methyl)-3-nitropyrazolo[1,5-*a*]pyrazine-4-carboxylate (3g)

A mixture of compound **2g** (1 g, 4.5 mmol) and silylformamidine **1** (2.13 g, 13.5 mmol) in benzene (7 mL) was stirred at r.t. for 30 min, and then at 50 °C for 10 min. After removal of excess silylformamidine under reduced pressure, the residue was recrystallized from hexane to afford aminal **3g**.

Yield: 77% (1.32 g); yellow crystals; mp 145–147 °C.

^{1}H NMR (400 MHz, C_6D_6): δ = 8.39 (s, 1 H), 7.95 (s, 1 H), 4.88 (s, 1 H), 3.69 (s, 3 H), 1.91 (s, 6 H), 1.83 (s, 3 H), 0.06 (s, 9 H).

^{13}C NMR (125 MHz, C_6D_6): δ = 163.9, 150.8, 144.6, 139.4, 134.3, 127.1, 74.7, 52.4, 48.3, 41.3, 26.8, –0.7.

Anal. Calcd for $C_{15}H_{24}N_6O_4Si$: C, 47.35; H, 6.36; N, 22.09. Found: C, 47.62; H, 6.29; N, 21.89.

Dimethyl 7-((Dimethylamino)(methyl(trimethylsilyl)amino)-methyl)pyrazolo[1,5-*a*]pyrazine-3,4-dicarboxylate (3h)

A mixture of compound **2h** (1 g, 4.3 mmol) and silylformamidine **1** (2.06 g, 13 mmol) was stirred at r.t. for 24 h. After removal of excess silylformamidine under reduced pressure, the residue was recrystallized from pentane to afford aminal **3h**.

Yield: 71% (1.19 g); yellowish crystals; mp 102–103 °C.

^{1}H NMR (400 MHz, C_6D_6): δ = 8.38 (s, 1 H), 8.28 (s, 1 H), 5.05 (s, 1 H), 3.80 (s, 3 H), 3.46 (s, 3 H), 1.96 (s, 6 H), 1.91 (s, 3 H), 0.11 (s, 9 H).

^{13}C NMR (150 MHz, C_6D_6): δ = 164.8, 161.7, 145.8, 144.1, 134.0, 132.4, 129.6, 106.1, 75.0, 52.2, 50.9, 41.4, 26.8, –0.6.

Anal. Calcd for $C_{17}H_{27}N_5O_4Si$: C, 51.89; H, 6.92; N, 17.80. Found: C, 51.97; H, 6.87; N, 17.97.

1-(2-Bromo-4-chloro-3-iodopyrazolo[1,5-*a*]pyrazin-7-yl)-*N*,*N*,*N*′-trimethyl-*N*′-(trimethylsilyl)methanediamine (3i)

A mixture of compound **2i** (1 g, 2.8 mmol) and silylformamidine **1** (1.33 g, 8.4 mmol) was heated to 80 °C for 15 min, kept at this temperature for 5 min, then cooled to r.t. After removal of excess silylformamidine under reduced pressure, the residue was recrystallized from hexane to afford aminal **3i**.

Yield: 82% (1.18 g); yellow crystals; mp 122–124 °C.

^{1}H NMR (400 MHz, C_6D_6): δ = 7.86 (s, 1 H), 4.81 (s, 1 H), 2.0 (s, 6 H), 1.92 (s, 3 H), 0.16 (s, 9 H).

^{13}C NMR (150 MHz, C_6D_6): δ = 140.9, 139.3, 134.5, 132.1, 127.4, 74.8, 57.9, 41.6, 26.9, –0.7.

Anal. Calcd for $C_{13}H_{20}BrClIN_5Si$: C, 30.22; H, 3.90; N, 13.55. Found: C, 29.87; H, 3.750; N, 13.24.

Synthesis of Aldehydes 4; General Procedure

Aminal **3** (3 mmol) was dissolved in aqueous 15% hydrochloric acid (2 mL). The reaction mixture was heated at 60 °C for 10 min with stirring. After cooling to r.t., the reaction mixture was extracted with dichloromethane (2 × 5 mL). The aqueous layer was separated, evaporated to dryness, washed with water (2 × 5 mL), and dried.

4-Oxo-4,5-dihydropyrazolo[1,5-*a*]pyrazine-7-carbaldehyde (4a)

Yield: 93% (460 mg); colorless crystals; mp 255–258 °C.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 12.12 (s, 1 H, NH), 9.88 (s, 1 H), 7.98 (s, 1 H), 7.81 (s, 1 H), 7.11 (s, 1 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 181.0, 155.3, 141.0, 132.8, 129.7, 120.2, 105.4.

Anal. Calcd for $C_7H_5N_3O_2$: C, 51.54; H, 3.09; N, 25.76. Found: C, 51.76; H, 2.89; N, 25.86.

Methyl 7-Formylpyrazolo[1,5-*a*]pyrazine-4-carboxylate (4c)

Yield: 83% (504 mg); yellow crystals; mp 161–163 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.68 (s, 0.3 H), 8.53, 8.44 (2 × s, 0.68 H), 8.33, 8.28 (2 × s 1.08 H), 7.45 (s, 0.39 H), 7.31 (s, 0.63 H), 7.12 (s, 0.69 H), 6.52 (s, 0.58 H), 4.01, 3.98 (2 × s, 3 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 184.5, 163.3, 162.7, 144.7, 143.7, 143.1, 140.4, 137.8, 135.0, 134.3, 130.6, 127.9, 124.6, 102.2, 100.6, 84.3, 53.1, 52.7.

Anal. Calcd for $C_9H_7N_3O_3$: C, 52.69; H, 3.44; N, 20.48. Found: C, 52.54; H, 3.65; N, 20.23.

Methyl 3-(Difluoromethyl)-7-formylpyrazolo[1,5-*a*]pyrazine-4-carboxylate (4e)

Yield: 87% (671 mg); yellow crystals; mp 147–149 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.7 (s, 0.8 H), 8.71 (s, 0.8 H), 8.60 (s, 1.8 H), 8.31 (s, 1 H), 7.51 (t, J = 56 Hz, 1 H), 7.2 (bs, 1.4 H), 6.51 (s, 1 H), 4.0 (s, 3 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 184.3, 163.9, 163.4, 145.5, 142.3, 141.8, 141.3, 138.2, 131.5, 131.1, 130.6, 128.1, 125.7, 113.2, 113.0, 11.7, 111.4, 110.1, 109.9, 109.7, 109.5, 108.6, 108.4, 108.2, 53.5, 53.2.

Anal. Calcd for $C_{10}H_7F_2N_3O_3$: C, 47.07; H, 2.77; N, 16.47. Found: C, 47.32; H, 2.87; N, 16.87.

Methyl 3-Bromo-7-formylpyrazolo[1,5-*a*]pyrazine-4-carboxylate (4f)

Aminal **3f** (1.23 g, 3 mmol) was dissolved in aqueous 20% hydrobromic acid (2 mL). The reaction mixture was heated at 60 °C for 10 min with stirring. After cooling to r.t., the reaction mixture was extracted with dichloromethane (3 × 10 mL), then all volatiles were evaporated and the residue was dissolved in diethyl ether (20 mL) upon heating. The solution was filtered and the volume was reduced to 1 mL and left for crystallization. The precipitated aldehyde was collected and dried.

Yield: 52% (440 mg); yellow crystals; mp 115–116 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.84 (s, 1 H), 8.50 (s, 1 H), 8.23 (s, 1 H), 4.13 (s, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 183.0, 162.8, 148.9, 144.9, 131.4, 131.1, 127.5, 89.7, 53.6.

Anal. Calcd for $C_9H_6BrN_3O_3$: C, 38.05; H, 2.13; N, 14.79. Found: C, 37.88; H, 1.98; N, 14.97.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_9H_6BrN_3O_3$: 283.9671; found: 283.9665.

Methyl 7-Formyl-3-nitropyrazolo[1,5-*a*]pyrazine-4-carboxylate (4g)

Yield: 80% (605 mg); yellow crystals; mp 150–151 °C (diethyl ether).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.94 (s, 1 H), 8.84 (s, 1 H), 8.77 (s, 1 H), 4.11 (s, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 181.6, 162.6, 149.2, 140.5, 132.6, 127.8, 126.2, 125.9, 53.4.

Anal. Calcd for $C_9H_6N_4O_5$: C, 43.21; H, 2.42; N, 22.40. Found: C, 43.43; H, 2.34; N, 22.34.

Dimethyl 7-Formylpyrazolo[1,5-*a*]pyrazine-3,4-dicarboxylate (4h)

Yield: 51% (400 mg); yellow crystals; mp 118–120 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.90 (s, 1 H), 8.63 (s, 1 H), 8.60 (s, 1 H), 4.10 (s, 3 H), 3.95 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 182.7, 163.5, 161.2, 150.3, 145.2, 131.7, 131.5, 126.6, 107.7, 53.1, 51.8.

Anal. Calcd for $C_{11}H_9N_3O_5$: C, 50.20; H, 3.45; N, 15.96. Found: C, 50.34; H, 3.61; N, 16.11.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_9N_3O_5$: 264.0621; found: 264.0616.

Synthesis of Methylimines; General Procedure

Aminal **3** (3 mmol) was dissolved in MeOH (20 mL) at 30 °C. After 30 min, the volume was reduced to 5 mL and the reaction mixture was left at –10 °C. The precipitated solid was collected by filtration, washed with cold MeOH (2 × 5 mL) and dried.

(*E*)-*N*-((4-Methoxypyrazolo[1,5-*a*]pyrazin-7-yl)methylene)methanamine (5b)

Aminal **3b** (0.7 g, 2.3 mmol) was dissolved in MeOH (10 mL). The reaction mixture was heated at 40 °C for 1 h. The solvent was evaporated and the residue was sublimated (0.1 Torr, oil bath at 130 °C).

Yield: 90% (387 mg); white solid; mp 116–118 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.88 (s, 1 H), 7.91 (s, 1 H), 7.86 (s, 1 H), 6.78 (s, 1 H), 4.07 (s, 3 H), 3.58 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 157.0, 152.8, 140.3, 127.6, 125.9, 124.5, 98.3, 53.6, 48.5.

Anal. Calcd for $C_9H_{10}N_4O$: C, 56.83; H, 5.30; N, 29.46. Found: C, 56.98; H, 5.67; N, 29.12.

Methyl (*Z*)-7-((Methylimino)methyl)-3-nitropyrazolo[1,5-*a*]pyrazine-4-carboxylate (5g)

Aminal **3g** (3 mmol) was dissolved in MeOH (20 mL) and heated at 60 °C for 30 min. The solution was then cooled to –20 °C and the precipitated solid was collected by filtration, washed with cold MeOH (2 × 5 mL), and dried.

Yield: 75% (600 mg); yellow crystals; mp 152–153 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.18 (s, 1 H), 8.83 (s, 1 H), 8.76 (s, 1 H), 4.08 (s, 3 H), 3.78 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.3, 150.8, 145.5, 140.1, 129.9, 129.1, 126.8, 126.2, 53.2, 49.0.

Anal. Calcd for $C_{10}H_9N_5O_4$: C, 45.63; H, 3.45; N, 26.61. Found: C, 45.37; H, 3.63; N, 26.34.

1-(2-Bromo-4-chloro-3-iodopyrazolo[1,5-*a*]pyrazin-7-yl)-*N*-methylmethanimine (5i)

Aminal **3i** (1.53 g, 3 mmol) was dissolved in MeOH (20 mL) and heated at 35 °C for 30 min. The volume was reduced to a half then the solution was cooled to –10 °C. The precipitated solid was collected by filtration, washed with cold MeOH (2 × 5 mL), and dried.

Yield: 68% (810 mg); yellow crystals; mp 187–189 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.90 (s, 1 H), 8.10 (s, 1 H), 3.61 (s, 3 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 152.3, 142.5, 139.9, 134.1, 128.7, 126.0, 61.9, 48.2.

Anal. Calcd for $C_8H_5BrClIN_4$: C, 24.06; H, 1.26; N, 14.03. Found: C, 23.69; H, 1.02; N, 13.78.

7-((2-Phenylhydrazono)methyl)pyrazolo[1,5-*a*]pyrazin-4(5*H*)-one (6a)

Aldehyde **4a** (50 mg, 0.3 mmol) was dissolved in MeOH (3 mL) and phenylhydrazine (65 mg, 0.6 mmol) was added and the reaction mixture was heated at 60 °C for 5 min. After cooling to r.t., the precipitated solid was collected by filtration, and dried.

Yield: 72% (56 mg); yellow crystals; mp 264–266 °C (decomp).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.55 (s, 1 H, NH), 10.64 (s, 1 H), 8.35 (s, 1 H), 7.98 (s, 1 H), 7.27 (s, 1 H), 7.22 (dd, *J* = 8, 8 Hz, 2 H), 7.08 (m, 3 H), 6.70 (dd, *J* = 8, 8 Hz, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 154.9, 144.8, 140.3, 133.2, 129.1, 126.4, 119.2, 118.8, 112.1, 111.4, 105.0.

Anal. Calcd for $C_{13}H_{11}N_5O$: C, 61.65; H, 4.38; N, 27.65. Found: C, 61.78; H, 4.12; N, 27.45.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{11}N_5O$: 254.1042; found: 254.10391.

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0043-1775378.

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