A Concise Microwave-Assisted Synthesis of 2-Aminoimidazole Marine Sponge Alkaloids of the Isonaamines Series

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Abstract: A short and efficient route to 1,4-substituted 2-aminoimidazole alkaloids starting from the easily accessible 2-alkylaminopyrimidines and α-bromo aldehydes is reported. The formation of the intermediate imidazo[1,2-*a*]pyrimidinium salts and subsequent cleavage were facilitated by microwave irradiation. Marine sponge alkaloids preclathridines A, C and isonaamines A, C, D were obtained in high yields using the optimized one-pot two-step procedure.

Key words: natural products, ring opening, cleavage, imidazo[1,2-*a*]pyrimidin-1-ium salts, 2-aminoimidazoles

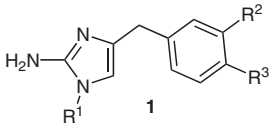
Marine sponges have been proven to be a source of biologically active alkaloids and their metabolites. Among the calcareous sponges, the genera *Leucetta* and *Clathrina* are a rich source of imidazole alkaloids. Since the first discovery of 2-aminoimidazole alkaloids in marine sponges by Kashman's group in 1987,[1] a number of preclathridine and isonaamine alkaloids, representing a family of 1,4-substituted 2-aminoimidazoles **1** bearing one or two substituted benzyl moieties, has been isolated and synthesized in the last two decades (Table 1).[2] Many 2-aminoimidazole alkaloids have been reported to have cytotoxic, antimicrobial, and antifungal properties.[3]

The reported synthetic approaches to 1,4-dialkyl-2-aminoimidazoles **1** include quite a lengthy iminophosphorane-mediated synthesis from α-azido esters,[4] the condensation of poorly available α-amino ketones with cyanamide,[5,6] or a multistep derivatization of the protected imidazole core.[7,8]

We have recently communicated a facile one-pot two-step procedure for the synthesis of diversely substituted 2-aminoimidazoles from α-bromocarbonyl compounds and substituted 2-aminopyrimidines.[11] This methodology could serve as a novel, practical, and general approach to marine alkaloids of the family **1** (Table 1).

Here, we report a short and efficient total synthesis of preclathridine and isonaamine alkaloids **1a–e** based on the condensation of 2-aminopyrimidines **3** and α-bromo aldehydes **4** and subsequent cleavage of the intermediate imidazopyrimidinium salts **2** (Scheme 1). Although heterocyclization reactions of α-bromo aldehydes are hardly known due to their high reactivity, in our preliminary studies we were able to synthesize several 1,4-disubstituted 2-aminoimidazoles in high yields applying a one-pot two-step microwave-assisted protocol.[11]

Table 1 1,4-Substituted 2-Aminoimidazole Marine Sponge Alkaloids



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Alkaloid	R^1	R^2	R^3	Isolated	Synthesis
Preclathridine A (**1c**)	Me	-OCH_2O-		1992[9]	1996,[7] 1999[4]
Preclathridine C (**1i**)	Me	H	OH	1991[5]	1991,[5] 1999[4]
Isonaamine A (**1j**)	4-Hydroxybenzyl	H	OH	1987[1a]	1999[4]
Isonaamine C (**1e**)	4-Methoxybenzyl	H	MeO	1992[9]	2003[8]
Isonaamine D (**1g**)	4-Hydroxybenzyl	H	MeO	1998[3d]	–
Isonaamine E (**1f**)	4-Methoxybenzyl	MeO	MeO	2002[10]	–

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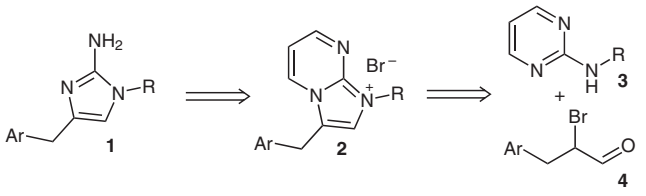


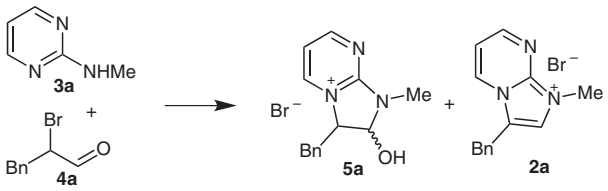
Scheme 1 Retrosynthetic analysis for the synthesis of 1,4-substituted 2-aminoimidazoles

The crucial step in the synthesis of 2-aminoimidazoles from 2-aminopyrimidines is the formation of imidazo[1,2-*a*]pyrimidin-1-ium salts **2** (Scheme 1).[11] As a proof of this concept, the cyclization step was initially optimized using 2-methylaminopyrimidine[12] (**3a**) and 1.35 equivalents of 2-bromo-3-phenylpropanal (**4a**) as starting materials (Table 2). At room temperature (or after reflux in MeCN) we observed the formation of stable hydrate **5a** instead of the expected aromatic salt **2a**. We carefully investigated the microwave-assisted dehydration of the intermediate salt **5a** to the dehydrated salt **2a**. A sealed vial containing a solution of the starting compounds **3a** and **4a** in acetonitrile was irradiated at 120–130 °C for 20–30 minutes (Table 2, entries 1–3). However, only trace amounts of the desired 1-methyl-3-benzylimidazo[1,2-*a*]pyrimidin-1-ium salt (**2a**) were observed next to the hydroxy salt **5a**. Upon further increasing the temperature to 140 °C, a nearly equimolar mixture of salts **5a** and **2a** was obtained (Table 2, entry 4). Increasing the ceiling temperature to 160 °C and the maximum power to 200 W for 25 minutes drove the reaction completely to the formation of the desired imidazo[1,2-*a*]pyrimidin-1-ium salt **2a** as the sole reaction product (Table 2, entry 6).

Having optimized the microwave-assisted protocol for the synthesis of 1,4-substituted 2-aminoimidazoles, we developed a short route for the related marine sponge alkaloids from readily available starting materials. 2-Benzylaminopyrimidine[13] (**3b**) and 2-(4-methoxybenzyl)aminopyrimidine (**3c**) were prepared from the corresponding amines and 2-chloropyrimidine (**6**) by microwave irradiation (Scheme 2). Subsequent demethylation of the methoxy group of compound **3c**, followed by silyl protection with *tert*-butyldimethylsilyl chloride, provided pyrimidine **8**.

For the synthesis of α-bromo aldehydes, the substituted 3-phenylpropanols **9a–d**, which can be easily accessed from the corresponding cinnamic acids,[14] were oxidized to the aldehydes **10a–d**.[15] Mild bromination[16] of **10a–d** using 0.5 equivalent of 5,5-dibromobarbituric acid (DBBA)[17] at room temperature resulted in the formation of the required

Table 2 Investigation of the Condensation under Conventional Heating and Microwave Irradiation Conditions[a]

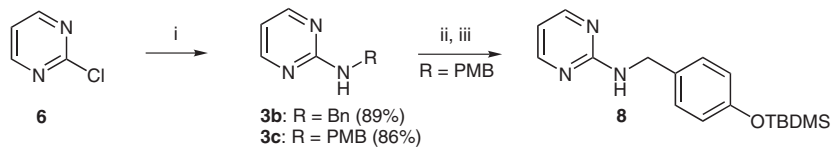


Entry	Temp (°C)	Time (min)	Power (W)[b]	Ratio **5a**:**2a**[c]
1	120	20	120	100:0
2	130	20	150	95:5
3	130	30	150	67:33
4	140	30	150	51:49
5	150	30	150	8:92
6	160	25	200	0:100

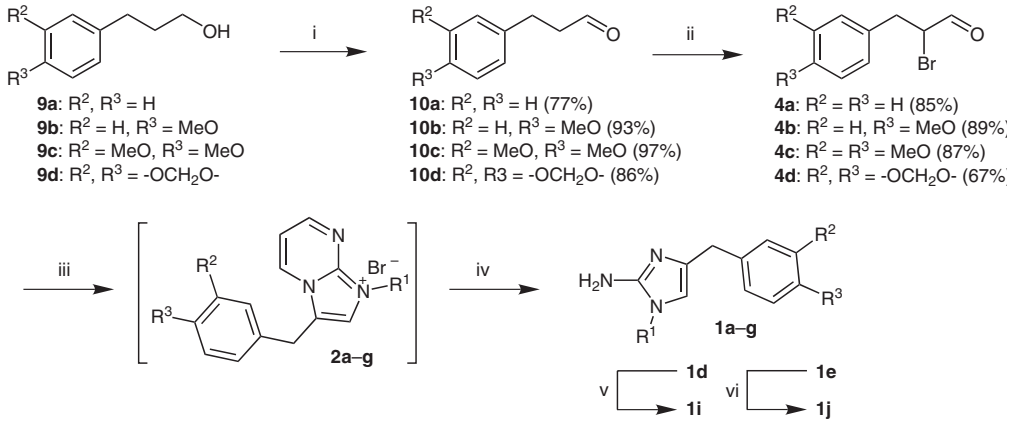
[a] All reactions were carried out on a 1 mmol scale of 2-methylaminopyrimidine (**3a**) with 2-bromo-3-phenylpropan-1-al (**4a**) (1.35 equiv) in MeCN (5 mL).
[b] Ceiling power of MW irradiation.
[c] Determined by ^{1}H NMR spectroscopy.

α-bromo aldehydes **4a–d** (Scheme 2). These were irradiated together with 2-alkylaminopyrimidines **3a–c** and **8** in acetonitrile at 80 °C for 10 minutes, and subsequently at 160 °C for 25 minutes, leading to the desired intermediates **2a–g**. The final step – cleavage of the pyrimidine fragment – was achieved by the addition of hydrazine hydrate (7 equiv) to the cooled reaction mixture, and irradiation was continued at 100 °C for another 10 minutes. The obtained 1,4-substituted 2-aminoimidazoles **1a–g** were isolated in good yields as shown in Table 3 (entries 1–7). Remarkably, we observed almost complete loss of the TBDMS group under the cleavage conditions (Table 3, entry 7) and 2-aminoimidazole **1g** was isolated in 58% yield together with 5% of the protected counterpart **1h**. The 2-aminoimidazoles **1d** and **1e** were demethylated with BBr_3 to give preclathridine A (**1i**) and isonaamine A (**1j**) in good yields (Table 3, entries 8 and 9).

Finally, the structure of synthetic isonaamine C (**1e**) was unambiguously confirmed by single crystal X-ray crystallography (Figure 1).[18] Interestingly, two hydrogen bonds (between amino groups and endocyclic nitrogen atoms) link two aminoimidazole molecules in the crystal into centrosymmetric dimers (with NH…N bond length 2.07 Å), similar to the effect we observed earlier[19] for 2-amino-1-methyl-5-(4-chlorophenyl)imidazole.



Scheme 2 *Reagents and conditions*: (i) amine (1.3 equiv), Et_3N (1.5 equiv), EtOH, MW 80 W, 120 °C, 5 min; (ii) BBr_3 (5 equiv), CH_2Cl_2, 0 °C to r.t., 12 h (→ **7**, 64%); (iii) TBDMSCl (1.25 equiv), imidazole (1.4 equiv), DMF, r.t., overnight (92%).



Scheme 3 *Reagents and conditions*: (i) PCC (1.4 equiv), CH_2Cl_2, 0 °C, 3–4 h; (ii) DBBA (0.5 equiv), Et_2O, HCl (cat.), r.t., 15–20 hr; (iii) 2-alkylaminopyrimidines **3a–c** and **8**, DMAP (cat.), MeCN, MW 200 W, 80 °C, 10 min, then 160 °C, 25 min; (iv) hydrazine hydrate (7 equiv), MW 100 W, 100 °C, 10 min; (v) BBr_3 (5 equiv), CH_2Cl_2, 0 °C to r.t., 0.5 h; (vi) BBr_3 (10 equiv), CH_2Cl_2, 0 °C to r.t., 1 h.

Table 3 2-Aminoimidazoles **1a–j** Prepared[a]

Entry	Product	R^1	R^2	R^3	Yield (%)[b]
1	**1a**	Me	H	Bn	88
2	**1b**	Bn	H	Bn	74
3	**1c**	Me	-OCH_2O-		67
4	**1d**	Me	H	MeO	87
5	**1e**	4-Methoxybenzyl	H	MeO	89
6	**1f**	4-Methoxybenzyl	MeO	MeO	85
7	**1g** + **1h**	4-Hydroxybenzyl + 4-TBDMSObenzyl	H	MeO	58 + 5
8	**1i**	Me	H	OH	55
9	**1j**	4-Hydroxybenzyl	H	OH	71

[a] Yields of 2-aminoimidazoles **1a–h** given for the one-pot procedure, starting from α-bromo aldehydes **4a–d**.
[b] Isolated yield.

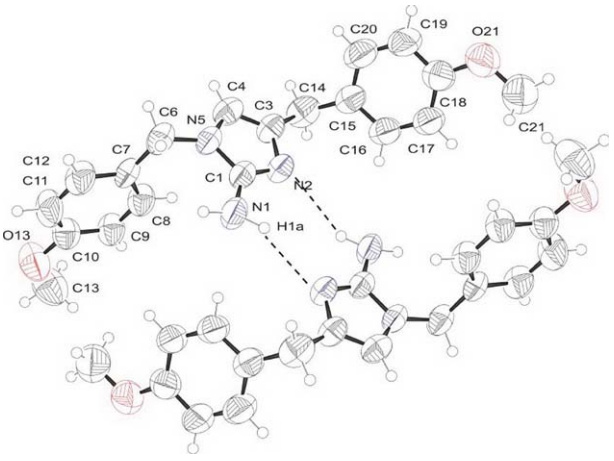


Figure 1 Crystal structure of isonaamine C

In conclusion, we have applied a short and efficient microwave-assisted protocol for the preparation of the 1,4-dialkyl-2-aminoimidazole-based marine sponge alkaloids, using readily available substituted 2-aminopyrimidines as the masked guanidine function[20] in the reaction with α-bromo aldehydes. In addition to its simplicity, this method provides high yields of products in short reaction times. The microwave-assisted procedure would be of great use in the synthesis of a range of 2-aminoimidazole-based natural products.

Melting points were determined using a Reichert-Jung Thermovar apparatus or an Electrothermal 9200 digital melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker Avance 300 (300/75.5 MHz) and 400 (400/100.5 MHz) instruments using $CDCl_3$ and DMSO-d_6 as solvents. The ^{1}H and ^{13}C chemical shifts are reported in parts per million relative to tetramethylsilane using the residual solvent signal as an internal reference. Mass spectra were recorded by using a Kratos MS 50 TC, Kratos Mach III system, and LCQ Advantage (Thermo Electron Corp.). The ion source temperature was 150–250 °C, as required. High-resolution EI-mass spectra were performed with a resolution of 10000. The low-resolution spectra were obtained with a HP5989A MS instrument. For TLC, analytical TLC plates [Alugram SIL G/UV_{254} and 70–230 mesh silica gel (E. M. Merck)] were used.

Microwave Experiments

A multimode Milestone MicroSYNTH microwave reactor (Laboratory Microwave Systems) was used in the standard configuration as delivered, including proprietary software. Reaction temperatures were monitored by an IR sensor on the outside wall of the reaction vial and a fiber optic sensor inside the reaction vial. All experiments were carried out in sealed microwave process vials (15, 50 mL). After completion of the reaction, the vial was cooled to 25 °C via air jet cooling before opening.

(4-Methoxybenzyl)pyrimidin-2-ylamine (3c)

In a 50 mL microwave vial, 2-chloropyrimidine (3.43 g, 30 mmol), 4-methoxybenzylamine (5.35 g, 39 mmol, 1.3 equiv), and Et_3N (6.2 mL, 45 mmol, 1.5 equiv) were successively dissolved in EtOH (20 mL). The reaction tube was sealed, and irradiated in the cavity of a microwave reactor at a ceiling temperature of 120 °C at 80 W maximum power for 5 min. After the mixture was cooled with an air flow for 15 min, it was diluted with H_2O (100 mL), extracted with CH_2Cl_2 (2 × 150 mL), and the combined organic extracts were dried

(Na_2SO_4). The solvent was removed under reduced pressure and the residue was subjected to silica gel flash chromatography (0–5% MeOH–CH_2Cl_2) to afford 5.55 g (86%) of **3c**; colorless solid; mp 101–102 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.26 (d, *J* = 4.8 Hz, 2 H), 7.26 (d, *J* = 8.6 Hz, 2 H), 6.86 (d, *J* = 8.5 Hz, 2 H), 6.54 (t, *J* = 4.8 Hz, 1 H), 5.50 (br, 1 H), 4.56 (d, *J* = 5.7 Hz, 2 H), 3.81 (s, 3 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 162.7, 159.3, 158.4 (2 ×), 131.6, 129.3 (2 ×), 114.4 (2 ×), 110.9, 55.7, 45.4.

HRMS-EI: *m*/*z* calcd for $C_{16}H_{21}N_3$ $[M]^+$: 215.1059; found: 215.1064.

4-(Pyrimidin-2-ylaminomethyl)phenol (7)
To a solution of **3c** (3.23 g, 15 mmol) in CH_2Cl_2 (50 mL) at 0 °C was added dropwise BBr_3 (7.2 mL, 75 mmol, 5 equiv) and the mixture was stirred at r.t. for 1 day. The mixture was cooled in an ice bath, and then 6 N ammonia in MeOH (~60 mL) was added carefully. The mixture was diluted with H_2O (200 mL), extracted with EtOAc (2 × 150 mL), and the combined organic extracts were dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was subjected to column chromatography on silica gel (from 10% MeOH–CH_2Cl_2) to afford 1.93 g (64%) of **7**; white solid; mp 183–185 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.22 (s, 1 H), 8.24 (d, *J* = 4.7 Hz, 2 H), 7.54 (t, *J* = 6.0 Hz, 1 H), 7.10 (d, *J* = 8.2 Hz, 2 H), 6.67 (d, *J* = 8.2 Hz, 2 H), 6.54 (t, *J* = 4.8 Hz, 1 H), 4.36 (d, *J* = 6.3 Hz, 2 H).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 163.1, 158.9, 158.8, 156.9, 131.4, 129.3, 115.8, 110.9, 44.3.

HRMS-EI: *m*/*z* calcd for $C_{16}H_{21}N_3$ $[M]^+$: 201.0902; found: 201.0892.

[4-(*tert*-Butyldimethylsilyloxy)benzyl]pyrimidin-2-yl-amine (8)
To a solution of **7** (1.4 g, 7 mmol) in DMF (25 mL) were added TBDMSCl (1.32 g, 8.75 mmol, 1.25 equiv) and imidazole (0.67 g, 9.8 mmol, 1.4 equiv), and the mixture was stirred overnight at r.t. After partition of the mixture between Et_2O (200 mL) and aq sat. $NaHCO_3$ (100 mL), the organic layer was washed with H_2O (50 mL) and brine (50 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified by flash chromatography on neutral alumina (CH_2Cl_2–Et_2O, 4:1) to afford 2.03 g (92%) of **8**; colorless solid; mp 132–134 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.28 (d, *J* = 4.2 Hz, 2 H), 7.21 (d, *J* = 8.3 Hz, 2 H), 6.80 (d, *J* = 8.6 Hz, 2 H), 6.55 (t, *J* = 4.7 Hz, 1 H), 5.49 (br, 1 H), 4.56 (d, *J* = 5.5 Hz, 2 H), 0.99 (s, 9 H), 0.20 (s, 6 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 162.7, 158.4 (2 ×), 155.3, 132.1, 129.3 (2 ×), 120.6 (2 ×), 111.0, 45.5, 26.1 (3 ×), 18.6, – 4.0 (2 ×).

HRMS-EI: *m*/*z* calcd for $C_{16}H_{21}N_3$ $[M]^+$: 315.1767; found: 315.1768.

Compounds 2a and 5a
In a 15 mL microwave vial, 2-methylaminopyrimidine (**3a**; 109 mg, 1 mmol) and 2-bromo-3-phenylpropanal (**4a**; 288 mg, 1.35 mmol, 1.35 equiv) were successively dissolved in MeCN. The reaction tube was flushed with argon, sealed, and irradiated in the cavity of a microwave reactor at 80 W and at a ceiling temperature specified in Table 2. After the mixture was cooled with an air flow for 10 min, it was diluted with H_2O (25 mL), and the precipitate was washed with a 1:1 mixture Et_2O–acetone (2 × 10 mL) and dried in vacuum.

3-Benzyl-2-hydroxy-1-methyl-1*H*,2*H*,3*H*-imidazo[1,2-*a*]pyrimidin-4-ium Bromide (5a) (Table 2, Entry 1)
White solid; mp 197–199 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.97 (m, 1 H), 8.81 (m, 1 H), 7.42–7.23 (m, 7 H), 5.32 (dd, *J* = 8.3, 1.8 Hz, 1 H), 4.93 (m, 1 H), 3.32 (s, 2 H), 3.08 (s, 3 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 168.9, 154.8, 148.5, 135.0, 130.6 (2 ×), 129.6 (2 ×), 128.3, 111.6, 86.1, 68.7, 37.8, 28.9.

3-Benzyl-1-methylimidazo[1,2-*a*]pyrimidin-1-ium Bromide (2a) (Table 2, Entry 6)
Colorless solid; mp 155–156 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.28 (m, 1 H), 9.12 (m, 1 H), 8.16 (s, 1 H), 7.74 (dd, *J* = 6.3, 4.8 Hz, 1 H), 7.38–7.30 (m, 5 H), 4.46 (s, 2 H), 4.01 (s, 3 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 157.9, 143.0, 137.2, 136.0, 129.7 (4 ×), 128.1, 125.1, 124.9, 114.4, 33.6, 29.1.

DEPT NMR (75.5 MHz, $CDCl_3$): δ = 157.9, 137.2, 129.7 (4 ×), 128.1, 125.1, 114.4, 80.0, 33.6, 29.1.

3-Aryl-2-bromopropanals 4a–d; 2-Bromo-3-phenylpropanal (4a); Typical Procedure
A solution of **10a** (1.34 g, 10 mmol) in Et_2O (10 mL) was added dropwise to a solution of DBBA (1.45 g, 5 mmol, 5 equiv) in Et_2O (40 mL). Then, a 4 N solution of HCl in 1,4-dioxane (0.25 mL, 1 mmol) was added dropwise and the mixture was stirred for 15 h at r.t. After partition of the mixture between Et_2O (150 mL) and aq sat. $NaHCO_3$ (100 mL), the organic layer was washed with H_2O (50 mL) and brine (50 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give a light yellow oil. The crude product was purified by flash chromatography on neutral alumina (CH_2Cl_2–Et_2O, 2:1) to afford 1.81 g (85%) of **4a**; light oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.51 (s, 1 H), 7.38–7.24 (m, 5 H), 4.47 (m, 1 H), 3.55–3.48 (m, 1 H), 3.24–3.16 (m, 1 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 192.3, 136.7, 129.7 (2 ×), 129.2 (2 ×), 127.8, 55.1, 38.4.

HRMS-EI: *m*/*z* calcd for C_9H_9BrO $[M]^+$: 211.9837; found: 211.9850.

2-Bromo-3-(4-methoxyphenyl)propanal (4b)
Yield: 89%; light oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.49 (s, 1 H), 7.19 (d, *J* = 8.4 Hz, 2 H), 6.86 (d, *J* = 8.4 Hz, 2 H), 4.86 (m, 1 H), 3.73 (s, 1 H), 3.39 (m, 1 H), 3.14 (m, 1 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 192.5, 159.3, 130.8 (2 ×), 128.6, 114.6 (2 ×), 55.7, 55.4, 37.7.

HRMS-EI: *m*/*z* calcd for $C_{10}H_{11}BrO_2$ $[M]^+$: 241.9942; found: 241.9939.

2-Bromo-3-(3,4-dimethoxyphenyl)propanal (4c)
Yield: 87%; light oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.48 (s, 1 H), 6.92–6.74 (m, 3 H), 4.43 (m, 1 H), 3.87 (s, 3 H), 3.86 (s, 3 H), 3.46–3.39 (m, 1 H), 3.17–3.10 (m, 1 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 192.5, 149.5, 148.8, 129.1, 121.9, 112.8, 111.7, 68.4, 56.3, 55.2, 38.1.

HRMS-EI: *m*/*z* calcd for $C_{11}H_{13}BrO_3$ $[M]^+$: 272.0048; found: 272.0043.

3-(1,3-Benzodioxol-5-yl)-2-bromopropanal (4d)
Yield: 67%; light oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.48 (s, 1 H), 6.75–6.68 (m, 3 H), 6.01 (s, 2 H), 4.42 (m, 1 H), 3.64–3.50 (m, 1 H), 3.18–3.09 (m, 1 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 192.0, 149.7, 148.5, 129.7, 121.6, 109.3, 108.7, 101.4, 58.7, 38.6.

HRMS-EI: *m/z* calcd for $C_{10}H_9BrO_3$ $[M]^+$: 255.9735; found: 255.9738.

Microwave-Assisted Synthesis of 1a–g; 4-(4-Benzylbenzyl)-1-methyl-1*H*-imidazol-2-ylamine (1a); Typical Procedure

A 10 mL microwave vial was successively charged with MeCN (10 mL), 2-methylaminopyrimidine (**3a**; 435 mg, 4 mmol), 2-bromo-3-phenylpropanal (**4a**; 1.15 g, 5.4 mmol, 1.35 equiv), and DMAP (5 mg, 0.04 mmol, 1 mol%). The reaction tube was sealed, and irradiated in a microwave reactor first at a ceiling temperature of 80 °C at 200 W maximum power for 10 min, and then at 160 °C at 200 W maximum power for 25 min. After the mixture was cooled with an air flow for 15 min, hydrazine hydrate (1.4 mL of a 64% solution, 28 mmol 7 equiv) was added, and the mixture was irradiated for another 10 min at a ceiling temperature of 100 °C at 100 W maximum power. The mixture was diluted with CH_2Cl_2 (150 mL), the CH_2Cl_2 layer was washed with aq sat. NH_4Cl (100 mL), brine (100 mL), and H_2O (2 × 100 mL) and dried (Na_2SO_4). After filtration and concentration, the resulting residue was purified by column chromatography (silica gel; CH_2Cl_2–MeOH, 9:1 with 3% Et_3N) to afford 659 mg (88%) of **1a**; light yellow solid; mp 66–68 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.28 (m, 4 H), 7.18 (m, 1 H), 6.09 (s, 1 H), 4.16 (br, 2 H), 3.76 (s, 2 H), 3.30 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 148.1, 140.8, 137.4, 129.3 (2 ×), 128.7 (2 ×), 126.3, 113.3, 35.4, 31.6.

HRMS-EI: *m/z* calcd for $C_{11}H_{13}N_3$ $[M]^+$: 187.1109; found: 187.1108.

1-Benzyl-4-(4-benzylbenzyl)-1*H*-imidazol-2-ylamine (1b)

Yield: 74%; light yellow solid; mp 124–125 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.30 (m, 7 H), 7.15 (m, 3 H), 6.19 (s, 1 H), 4.80 (s, 2 H), 4.19 (br, 2 H), 3.80 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 148.4, 140.8, 137.5, 136.8, 129.4, 128.7, 128.3, 127.2, 126.3, 112.8, 48.8, 35.4.

DEPT NMR (75 MHz, $CDCl_3$): δ = 129.4 (2 × 2), 129.3 (2 × 2), 128.7 (2 × 2), 128.4, 127.2 (2 × 2), 126.3, –48.9, –35.4.

HRMS-EI: *m/z* calcd for $C_{17}H_{17}N_3$ $[M]^+$: 263.1422; found: 263.1425.

4-(1,3-Benzodioxol-5-ylmethyl)-1-methyl-1*H*-imidazol-2-ylamine (1c)

Yield: 87%; yellow oil.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.78 (m, 2 H), 6.68 (dd, *J* = 8.0, 0.9 Hz, 1 H), 6.19 (s, 1 H), 5.94 (s, 2 H), 5.45 (br, 2 H), 3.57 (s, 2 H), 2.67 (s, 3 H).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 151.7, 148.0, 146.3, 133.8, 121.9, 112.4, 109.6, 108.5, 107.0, 101.2, 33.6, 30.9.

HRMS-EI: *m/z* calcd for $C_{12}H_{13}N_3O_2$ $[M]^+$: 231.1008; found: 231.1008.

4-(4-Methoxybenzyl)-1-methyl-1*H*-imidazol-2-ylamine (1d)

Yield: 67%; light brown solid; mp 134–136 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.11 (d, *J* = 8.4 Hz, 2 H), 6.80 (d, *J* = 8.4 Hz, 2 H), 6.12 (s, 1 H), 5.19 (br, 2 H), 3.70 (s, 3 H), 3.49 (s, 2 H), 3.22 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 157.9, 147.7, 136.9, 132.3, 129.8, 113.8, 112.7, 55.3, 33.9, 31.3.

HRMS-EI: *m/z* calcd for $C_{12}H_{15}N_3O$ $[M]^+$: 217.1215; found: 263.1218.

1,4-Bis-(4-methoxybenzyl)-1*H*-imidazol-2-ylamine (1e)

Yield: 89%; colorless solid; mp 139–141 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.81 (br, 1 H), 7.13 (m, 4 H), 6.87 (d, *J* = 8.4 Hz, 2 H), 6.79 (d, *J* = 8.2 Hz, 2 H), 6.26 (s, 1 H), 6.12 (s, 1 H), 5.35 (s, 2 H), 4.76 (s, 2 H), 3.71 (s, 3 H), 3.69 (s, 3 H).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 159.4, 158.2, 149.6, 137.2, 133.8, 130.8, 130.4 (2 ×), 129.7 (2 ×), 114.7 (2 ×), 114.3 (2 ×), 110.9, 105.1, 55.9, 55.8, 47.3, 34.6.

HRMS-EI: *m/z* calcd for $C_{20}H_{23}N_3O_3$ $[M]^+$: 323.1634; found: 323.1631.

4-(3,4-Dimethoxybenzyl)-1-(4-methoxybenzyl)-1*H*-imidazol-2-ylamine (1f)

Yield: 85%; brown oil.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.19 (d, *J* = 8.0 Hz, 2 H), 6.80 (m, 5 H), 6.17 (s, 1 H), 4.58 (br, 2 H), 4.24 (s, 2 H), 3.83 (s, 3 H), 3.80 (s, 3 H), 3.77 (s, 3 H), 3.68 (s, 2 H).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 158.9, 150.3, 148.8, 147.5, 131.8, 131.7, 130.5, 128.5, 120.7, 114.0, 112.1, 111.8, 111.2, 55.9, 55.8, 55.2, 47.2, 32.6.

DEPT NMR (75.5 MHz, DMSO-d_6): δ = 128.8, 121.0, 114.3, 112.5, 112.2, 11.6, 56.3, 56.2, 55.6, –47.5, –32.96.

HRMS-EI: *m/z* calcd for $C_{20}H_{23}N_3O_3$: $[M]^+$: 353.1739; found: 353.1736.

4-[2-Amino-4-(4-methoxybenzyl)-1*H*-imidazol-1-ylmethyl]phenol (1g)

Yield: 58%; yellow solid; mp 155–157 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.33 (br, 1 H), 7.11 (d, *J* = 8.6 Hz, 2 H), 7.02 (d, *J* = 8.2 Hz, 2 H), 6.79 (d, *J* = 8.6 Hz, 2 H), 6.70 (d, *J* = 8.2 Hz, 2 H), 6.10 (s, 1 H), 5.23 (s, 2H), 4.70 (s, 2 H), 3.70 (s, 3 H), 3.49 (s, 2 H).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 157.3, 156.6, 148.6, 136.2, 132.9, 129.6 (2 ×), 128.9 (2 ×), 128.2, 115.2 (2 ×), 113.4 (2 ×), 110.0, 55.0, 46.5, 33.7.

HRMS-EI: *m/z* calcd for $C_{18}H_{19}N_3O_2$ $[M]^+$: 309.1477; found: 309.1482.

1-[4-(*tert*-Butyldimethylsilyloxy)benzyl]-4-(4-methoxybenzyl)-1*H*-imidazol-2-ylamine (1h)

Yield: 5%; white solid; mp 115–117 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.09 (m, 4 H), 6.80 (m, 4 H), 6.12 (s, 1 H), 5.30 (br, 2 H), 4.74 (s, 2 H), 3.69 (s, 3 H), 3.49 (s, 2 H), 0.93 (s, 9 H), 0.16 (s, 6 H).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 158.0, 155.8, 149.4, 137.7, 130.3, 129.9, 128.3, 120.7, 114.1, 113.9, 112.7, 108.1, 55.4, 48.3, 34.2, 25.8, 18.3, –4.3.

HRMS-EI: *m/z* calcd for $C_{24}H_{23}N_3O_2Si$ $[M]^+$: 423.2342; found: 423.2353.

O-Demethylation of 2-Aminoimidazoles 1d,e; 4-(2-Amino-1-methyl-1*H*-imidazol-4-ylmethyl)phenol (1i); Typical Procedure

To a solution of **1d** (326 mg, 1.5 mmol) in anhyd CH_2Cl_2 (10 mL) was added dropwise a 1 M solution of BBr_3 in CH_2Cl_2 (7.5 mL per methoxy group, 7.5 mmol, 5 equiv) at r.t. and the mixture was refluxed for 1 h at 55 °C. The reaction vessel was cooled in an ice bath and the reaction was quenched by the addition of 6 N ammonia in MeOH (7 mL). After evaporation of the solvent, the residue was subjected to column chromatography (20% MeOH–CH_2Cl_2) on silica gel basified with ammonia, to afford 167 mg (55%) of compound **1i**; yellow solid; mp 114–116 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.05 (br, 1 H), 6.99 (d, *J* = 8.4 Hz, 2 H), 6.62 (d, *J* = 8.4 Hz, 2 H), 6.10 (s, 1 H), 5.16 (s, 2H), 3.44 (s, 2 H), 3.22 (s, 3 H).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 154.9, 147.6, 135.5, 129.8, 128.9, 114.5, 111.5, 32.9, 30.5.

HRMS-EI: *m*/*z* calcd for $C_{11}H_{13}N_3O$ $[M]^+$: 203.1059; found: 203.1059.

4-[2-Amino-1-(4-hydroxybenzyl)-1*H*-imidazol-4-ylmethyl]phenol (1j)

Prepared from **1e**, following the procedure given above; yield: 71%; yellow solid; mp 125–127 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.31 (br, 1 H), 9.03 (br, 1 H), 7.01 (d, *J* = 8.3 Hz, 2 H), 6.98 (d, *J* = 8.4 Hz, 2 H), 6.69 (d, *J* = 8.5 Hz, 2 H), 6.61 (d, *J* = 8.3 Hz, 2 H), 6.07 (s, 1 H), 5.21 (s, 2 H), 4.88 (s, 2 H), 3.43 (s, 2 H).

^{13}C NMR (100.5 MHz, DMSO-d_6): δ = 156.7, 155.3, 148.5, 136.2, 130.9, 129.5 (2 ×), 128.9 (2 ×), 128.0, 115.2 (2 ×), 114.8 (2), 110.1, 46.6, 33.6.

HRMS-EI: *m*/*z* calcd for $C_{17}H_{17}N_3O_2$ $[M]^+$: 295.1321; found: 295.1327.

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(18) Crystallographic data for **1e** reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC 679428. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB 2 1EZ, UK [fax: +44(1223)336033 or E-mail: deposit@ccdc.cam.ac.uk]. Some selected crystallographic data: crystal system, space group: crystal system triclinic; space group $P\bar{1}$; cell parameters: *a* = 5.8703(16), *b* = 9.0133(8), *c* = 16.155(2) Å; α = 93.778(9), β = 91.640(10), γ = 94.461(10)°; V = 849.843 Å^3; Z = 2, Z′ = 0; R-factor 4.9%.

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