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-alkylamino-2-pyrimidines and a-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 a-azido esters,4 the condensation of poorly available a-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 a-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 a-bromo aldehydes 4 and subsequent cleavage of the intermediate imidazopyrimidinium salts 2 (Scheme 1). Although heterocyclization reactions of a-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

<table>
<thead>
<tr>
<th>Alkaloid</th>
<th>R1</th>
<th>R2</th>
<th>R3</th>
<th>Isolated</th>
<th>Synthesis</th>
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</thead>
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<tr>
<td>Isonaamine A</td>
<td>4-Hydroxybenzyl</td>
<td>H</td>
<td>OH</td>
<td>1987</td>
<td>1999</td>
</tr>
<tr>
<td>Isonaamine C</td>
<td>4-Methoxybenzyl</td>
<td>H</td>
<td>MeO</td>
<td>1992</td>
<td>2003</td>
</tr>
<tr>
<td>Isonaamine D</td>
<td>4-Hydroxybenzyl</td>
<td>H</td>
<td>MeO</td>
<td>1998</td>
<td>–</td>
</tr>
<tr>
<td>Isonaamine E</td>
<td>4-Methoxybenzyl</td>
<td>MeO</td>
<td>MeO</td>
<td>2002</td>
<td>–</td>
</tr>
</tbody>
</table>
The crucial step in the synthesis of 2-aminoimidazoles from 2-aminopyrimidines is the formation of imida-
zo[1,2-a]pyrimidin-1-ium salts 2 (Scheme 1). As a 
proof of this concept, the cyclization step was initially op-
timized using 2-methylaminopyrimidine12 (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 hy-
droxy salt 5a. Upon further increasing the irradiating 
temperature to 140 °C, a nearly equimolar mixture of salts 5a 
and 2a was observed (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-Benzyl-
aminopyrimidine13 (3b) and 2-(4-methoxybenzyl)aminopy-
rimidine (3c) were prepared from the corresponding 
amines and 2-chloropyrimidine (6) by microwave irradiation 
(Scheme 2). Subsequent demethylation of the meth-
xy group of compound 3c, followed by silyl protection with 
tert-butylidimethylsilyl chloride, provided pyrimi-
dine 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 bromination16 of 10a–d using 
0.5 equivalent of 5,5-dibromobarbituric acid (DBBA)17 at 
room temperature resulted in the formation of the required 
α-bromo aldehydes 4a–d (Scheme 2). These were irradi-
ated 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 hy-
drate (7 equiv) to the cooled reaction mixture, and irradi-
ation 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 BBr3 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 crystal-
llography (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 earlier19 for 2-amino-
1-methyl-5-(4-chlorophenyl)imidazole.

### Table 2 Investigation of the Condensation under Conventional Heating and Microwave Irradiation Conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temp (°C)</th>
<th>Time (min)</th>
<th>Power (W)b</th>
<th>Ratio 5a:2a+c</th>
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<td>20</td>
<td>120</td>
<td>100:0</td>
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<tr>
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<td>20</td>
<td>150</td>
<td>95:5</td>
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<td>3</td>
<td>130</td>
<td>30</td>
<td>150</td>
<td>67:33</td>
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<tr>
<td>4</td>
<td>140</td>
<td>30</td>
<td>150</td>
<td>51:49</td>
</tr>
<tr>
<td>5</td>
<td>150</td>
<td>30</td>
<td>150</td>
<td>8:92</td>
</tr>
<tr>
<td>6</td>
<td>160</td>
<td>25</td>
<td>200</td>
<td>0:100</td>
</tr>
</tbody>
</table>

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α-bromo aldehydes 4a–d (Scheme 2). These were irradi-
ated 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 
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Å), similar to the effect we observed earlier19 for 2-amino-
1-methyl-5-(4-chlorophenyl)imidazole.

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**Scheme 1** Retrosynthetic analysis for the synthesis of 1,4-substitu-
ted 2-aminoimidazoles

**Scheme 2** Reagents and conditions: (i) amine (1.3 equiv), Et3N (1.5 equiv), EtOH, MW 80 W, 120 °C, 5 min; (ii) BBr3 (5 equiv), CH2Cl2, 
0 °C to r.t., 12 h (~7, 64%); (iii) TBDMSCl (1.25 equiv), imidazole (1.4 equiv), DMF, r.t., overnight (92%).

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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 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. 1H NMR spectra were recorded on a Bruker Avance 300 (300/75.5 MHz) and 400 (400/100.5 MHz) instruments using CDCl3 and DMSO-d6 as solvents. The 1H and 13C 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 Et3N (6.2 mL, 45 mmol, 1.5 equiv) were successively dissolved in CH2Cl2 (2 × 150 mL), and the combined organic extracts were dried

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Table 3 2-Aminoimidazoles 1a–j Prepared

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>R1</th>
<th>R2</th>
<th>R3</th>
<th>Yield (%)</th>
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<td>Me</td>
<td>H</td>
<td>Bn</td>
<td>88</td>
</tr>
<tr>
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<td>1b</td>
<td>Bn</td>
<td>H</td>
<td>Bn</td>
<td>74</td>
</tr>
<tr>
<td>3</td>
<td>1c</td>
<td>Me</td>
<td>-OCH2O-</td>
<td>67</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1d</td>
<td>Me</td>
<td>H</td>
<td>MeO</td>
<td>87</td>
</tr>
<tr>
<td>5</td>
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<td>4-Methoxybenzyl</td>
<td>H</td>
<td>MeO</td>
<td>89</td>
</tr>
<tr>
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<td>1f</td>
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<td>MeO</td>
<td>MeO</td>
<td>85</td>
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<tr>
<td>7</td>
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<td>4-Hydroxybenzyl</td>
<td>H</td>
<td>MeO</td>
<td>58</td>
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<td>+</td>
<td>+</td>
<td>+</td>
<td>5</td>
</tr>
<tr>
<td>1h</td>
<td>4-TBDMSObenzyl</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>5</td>
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<td>1i</td>
<td>Me</td>
<td>H</td>
<td>OH</td>
<td>55</td>
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<tr>
<td>9</td>
<td>1j</td>
<td>4-Hydroxybenzyl</td>
<td>H</td>
<td>OH</td>
<td>71</td>
</tr>
</tbody>
</table>

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

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Figure 1 Crystal structure of isonaamine C
(Na₂SO₄). The solvent was removed under reduced pressure and the residue was subjected to silica gel flash chromatography (0–5% MeOH–CH₂Cl₂) to afford 5.55 g (86%) of 3c: colorless solid; mp 101–102 °C.

1H NMR (300 MHz, CDCl₃): 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).

13C NMR (75.5 MHz, CDCl₃): δ = 162.7, 159.3, 158.4 (2 ×), 131.6, 129.3 (2 ×), 114.4 (2 ×), 110.9, 55.7, 45.4.


3-Benzyl-1-methylimidazo[1,2-a]pyrimidin-1-ium Bromide (10a) (Table 2, Entry 1)

A solution of 10a (1.34 g, 10 mmol) in Et₂O (10 mL) was added dropwise to a solution of DBBA (1.45 g, 5 mmol, 5 equiv) in Et₂O (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 Et₂O (150 mL) and aq sat. NaHCO₃ (100 mL), the organic layer was washed with H₂O (50 mL) and brine (50 mL), dried (MgSO₄), and concentrated under reduced pressure to give a light yellow oil. The crude product was purified by flash chromatography on neutral alumina (CH₂Cl₂–Et₂O, 2:1) to afford 1.81 g (85%) of 10a: light oil.

1H NMR (300 MHz, CDCl₃): δ = 9.49 (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).

13C NMR (75.5 MHz, CDCl₃): δ = 129.2, 136.7, 129.7 (2 ×), 129.2 (2 ×), 127.8, 55.1, 38.4.

HRMS-EI: m/z calcd for C₁₆H₁₃BrO [M⁺]: 211.9837; found: 211.9850.

2-Bromo-3-(4-methoxyphenyl)propanol (4b)

Yield: 89%; light oil.

1H NMR (300 MHz, CDCl₃): 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).

13C NMR (75.5 MHz, CDCl₃): δ = 129.5, 159.3, 130.8 (2 ×), 128.6, 114.6 (2 ×), 55.7, 54.4, 37.7.

HRMS-EI: m/z calcd for C₁₆H₁₃BrO [M⁺]: 241.9942; found: 241.9939.

2-Bromo-3-(3,4-dimethoxyphenyl)propanol (4c)

Yield: 87%; light oil.

1H NMR (300 MHz, CDCl₃): 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).

13C NMR (75.5 MHz, CDCl₃): δ = 129.5, 149.5, 148.8, 129.1, 121.9, 112.8, 67.8, 56.4, 55.2, 38.1.

HRMS-EI: m/z calcd for C₁₆H₁₁BrO [M⁺]: 272.0048; found: 272.0043.

3-(1,3-Benzodioxol-5-yl)-2-bromopropanol (4d)

Yield: 67%; light oil.

1H NMR (300 MHz, CDCl₃): 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).

13C NMR (75.5 MHz, CDCl₃): δ = 129.0, 149.7, 148.5, 129.7, 121.6, 109.3, 108.7, 101.4, 58.7, 38.6.
Microwave-Assisted Synthesis of 1a–g; 4-(4-Benzylbenzyl)-1-methyl-1H-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-phenylpropanol (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 100 °C at 100 W maximum power for 20 min. After the mixture was cooled with an air flow for 15 min, hydrazine hydrate (1 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 CH2Cl2 (150 mL), the CH2Cl2 layer was washed withaq sat. NH4Cl (100 mL), brine (100 mL), and H2O (2 × 100 mL) and dried (Na2SO4). After filtration and concentration, the resulting residue was purified by column chromatography (silica gel; CH2Cl2–MeOH, 9:1 with 3% Et3N) to afford 659 mg (88%) of 1a, light yellow solid; mp 66–68 °C.

1H NMR (300 MHz, DMSO-d6): 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).

13C NMR (75 MHz, DMSO-d6): δ = 138.4, 134.0, 129.7, 129.3, 128.7 (2 ×), 126.3, 113.3, 35.4, 31.6.

HRMS-EI: m/z calcld for C14H13N3O2 [M]+: 231.1008; found: 231.1008.

Yield: 74%; light yellow solid; mp 126–128 °C.

1H NMR (300 MHz, CDCl3): 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).

13C NMR (75 MHz, CDCl3): δ = 134.8, 140.8, 137.5, 136.8, 129.4, 128.7, 123.7, 126.3, 112.8, 48.8, 35.4.

DEPT NMR (75 MHz, CDCl3): δ = 129.4 (2 ×), 129.3 (2 ×), 128.7 (2 ×), 128.4, 127.2 (2 ×), 126.3, −48.9, −35.4.

HRMS-EI: m/z calcld for C14H13N3O2 [M]+: 231.1008; found: 231.1008.

4-(3,4-Dimethoxybenzyl)-1-(4-methoxybenzyl)-1H-imidazol-2-ylamine (1i); Typical Procedure

To a solution of 1d (326 mg, 1.5 mmol) in anhyd CH2Cl2 (10 mL) was added dropwise a 1 M solution of BBr3 in CH2Cl2 (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 H2O (2 mL). After evaporation of the solvent, the residue was subjected to column chromatography (20% MeOH–CH2Cl2) on silica gel basified with ammonia, to afford 167 mg (55%) of compound 1i, light yellow solid; mp 112–114 °C.

1H NMR (300 MHz, DMSO-d6): 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).

13C NMR (75.5 MHz, DMSO-d6): 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 calcld for C20H17N5O3 [M]+: 323.1634; found: 323.1631.
13C NMR (75.5 MHz, DMSO-d6): δ = 154.9, 147.6, 135.5, 129.8, 128.9, 114.5, 111.5, 32.9, 30.5.


4-[2-Amino-1-(4-hydroxybenzyl)-1H-imidazol-4-ylmethyl]phenol (1j)
Prepared from 1e, following the procedure given above; yield: 71%; yellow solid; mp 125–127 °C.

1H NMR (400 MHz, DMSO-d6): 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).

13C NMR (100.5 MHz, DMSO-d6): δ = 156.7, 155.3, 148.5, 136.3, 130.9, 129.5 (2 ×), 128.9 (2 ×), 128.0, 115.2 (2 ×), 114.8 (2), 110.1, 46.6, 33.6.


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References
(2) To avoid contradictory assignment of the same names to the different isoaamidinoids, every isoaamidine was named in accordance with the parent isolated isoaamidine, as was originally proposed by Y. Kashman et al.1
(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 P1; cell parameters: a = 5.8703(16), b = 9.0133(8), c = 16.152(2) Å; α = 93.778(9), β = 91.640(10), γ = 94.461(10); V = 849.843 Å³; Z = 2, Z’ = 0; R-factor 4.9%.
(20) For analogous methodology to use the readily available pyrimidine-2-one as the masked urea function to prepare 2-aminoxazoles, see: Alifanov, V. L.; Babaev, E. V. Synthesis 2007, 263.