Syntheses of Pyrazine-, Quinoxaline-, and Imidazole-Fused Pyrroline Nitroxides

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Dedicated to the memory of Prof. Kálmán Hideg

A synthesis of a new diamagnetic synthon, 1-methoxy-2,2,5,5-tetramethylpyrrolidine-3,4-dione, was developed. Condensation of this compound with aliphatic or aromatic 1,2-diamines followed by deprotection yielded pyrroline nitroxide-fused pyrazines, pteridines, or quinoxalines, demonstrated on 7 examples in 15–39% overall yield over 2 or 3 steps. Reaction of the diamagnetic 1,2-diketone with an aldehyde and ammonium acetate produced a pyrrolo[3,4-d]imidazole scaffold in the Debus–Radziszewski reaction.

Key words free radicals, CH functionalization, oxidation, pyrazines, protecting groups

One of the main groups of long-lived stable radicals is the nitroxide (aminoxyl) radicals.1 Extensive studies of stable nitroxide free radicals first appeared 60 years ago, and their application is rather diverse and extends beyond spin labeling.2 They are used as co-oxidants in organic chemistry,3 building blocks for magnetic materials,4 superoxide dismutase mimics,5 antiproliferative compounds,6 mediators of polymerization,7 redox active materials in batteries,8 and magnetic resonance imaging (MRI)9 as well as electron paramagnetic resonance imaging (EPRI)10 contrast agents. These applications demand various scaffolds with diverse substitution patterns on pyrroline and piperidine nitroxides, including condensation with miscellaneous carbocycles and heterocycles. Synthesis of pyrroline nitroxide-fused carbocycles and heterocycles is one of the main activities of our laboratory, such as the synthesis of pyridazine-11 and pyrimidine-fused12 nitroxides (Figure 1). The latter was used in environmental studies investigating the distribution of sulfadiazine in a humic acid model system.13

Until now, we could not find a method for the synthesis of pyrazine (1,4-diazine)-fused pyrroline nitroxide. Pyrazines are important structural motifs of many biologically active molecules, such as riboflavin, and drugs such as pyrazinamide (antituberculotics) and varenicline (stop-smoking drug) (Figure 2).

It was obvious that the condensation of 1,2-diamines with paramagnetic 1,2-diketones suggests a synthetic route to novel paramagnetic 1,4-diazines and quinoxalines.14,15 Inspired by the work of Sandris and Ourisson,16 we attempted the synthesis of 1-oxyl-2,2,5,5-tetramethylpyrroline-3,4-dione by SeO2 oxidation of 1-oxyl-2,2,5,5-tetramethylpyrroline-3-one (1)17 (Scheme 1); however, no reaction occurred, and only starting material was recovered.

Based on our previous findings regarding sluggish reactions, we proposed that the free radical moiety must be protected; however, neither the N–OAc protection18 nor the hydroxylamine HCl salt form was sufficient for camouflaging...
The nitroxide moiety in the oxidation reaction with SeO₂. For nitroxide protection, we used the O-methylation technique by a Fenton reaction in the presence of DMSO, which was worked out in Bottle’s group. Treatment of compound 1 with a methyl radical generating system (Fe²⁺ and aq H₂O₂ mixture in DMSO) yielded compound 2, which could be oxidized smoothly by refluxing with 1.5 equivalents of SeO₂ in AcOH to afford compound 3 in a 63% yield over two steps (Scheme 2). Deprotection of compound 3 with 3-chloroperbenzoic acid (m-CPBA) gave an unstable five-membered diketo nitroxide compound, which decomposed during purification.

Alternatively, we returned to the Sandris and Ourisson method, but instead of an N-acetyl derivative, the NH functionality was protected with a readily hydrolyzable trifluoroacetyl group, and thus, compound 4 was treated with trifluoroacetic anhydride to give compound 5 in an 82% yield. Compound 5 could also be oxidized to diketo compound 6 in a 65% yield with SeO₂ in AcOH, but it was unstable and the crude product was used immediately in the next step. The diketo compounds 3 and 6 were condensed with 1,2-diaminobenzene (7a) to furnish pyrrolo[3,4-b]quinoxalines 7b and 8, respectively. Treatment of compound 7b with m-CPBA in dichloromethane (DCM) yielded nitroxide 7c. Compound 7c was also available via hydrolysis of compound 8 with aqueous KOH in EtOH, which produced compound 9 with prolonged reaction time and in a low (32%) yield. Compound 9 was then oxidized with m-CPBA in DCM to furnish 7c in a 13% yield over three steps (Scheme 3).

Considering the instability of the diketo compound 6 and the fact that the deprotection of the sterically hindered trifluoroacetamido group required harsh basic conditions, which is not compatible with many functional groups and its troublesome application (reduction of nitroxide, trifluoroacetylation, oxidation, condensation, hydrolysis of the trifluoroacetyl group, and restoring nitroxide function), in the following work, we used the O-methylation procedure, followed by oxidation, condensation, and mild deprotection with m-CPBA. Thus, we preferred compound 3 as the main building block instead of compound 6. In analogous reactions, compound 3 was condensed with different aromatic and heteroaromatic 1,2-diamino compounds such as 2,3-diaminobenzene (10a), 1,2,4,5-tetraaminobenzene (11a), 4,5-diaminopyrimidine (12a), 5,6-diaminouracil (13a) in ethanol, glacial acetic acid, or aqueous methanol to give the pyrazine ring condensed polycyclic compounds 10b, 11b, 12b, and 13b, respectively. Deprotection of 10b with m-CPBA gave the paramagnetic 5-carboxamidoquinoxaline 10c, which can be regarded as a potential poly (ADP-ribose) polymerase (PARP) inhibitor, and deprotection of compound 11b offered the rigid biradical compound 11c giving a quintet line in the EPR spectrum (see the Supporting Information [SI]). Deprotection of compound 12b furnished the paramagnetic pteridine 12c, and deprotection of compound 13b offered the paramagnetic pteridine-2,4(3H,8H)-dione 13c, the spin-labeled (SL) lumazine (Table 1).

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To construct the pyrrolo[3,4-b]pyrazine scaffold, compound 3 was condensed with 1,2-diaminoethane (14) yielding compound 15. Aromatization of 15 by treatment with 2.0 equivalents of sodium ethoxide in methanol at reflux temperature followed by standing overnight yielded the pyrazine-condensed precursor 16, which was deprotected with m-CPBA to give compound 17 in a 30% yield over three steps. Upon prolonged reaction time and excess m-CPBA (5.0 equiv) the formation of N-oxide 18 was observed, which could be arylated at the C2-position by palladium catalysis with benzene as a reaction solvent to give compound 19 in a 38% yield (Scheme 4).

To achieve the paramagnetic analogue of the antitubercular drug pyrazinamide, a condensation reaction of compound 3 was conducted with ethyl 2,3-diaminopropionic acid HCl salt 20 in EtOH with 4.0 equivalents of sodium

<table>
<thead>
<tr>
<th>Entry</th>
<th>1,2-Diamino compound</th>
<th>Diamagnetic product</th>
<th>Paramagnetic product</th>
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</thead>
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<tr>
<td>1</td>
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<td>4</td>
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*a* Reflux in AcOH,  
*b* Reflux in MeOH–H2O.

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**Table 1** Synthesis of Pyrazine Condensed Paramagnetic Polycyclic Compounds

<table>
<thead>
<tr>
<th>Entry</th>
<th>1,2-Diamino compound</th>
<th>Diamagnetic product</th>
<th>Paramagnetic product</th>
</tr>
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<tbody>
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<td>1</td>
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<td>10c</td>
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<td>12c</td>
</tr>
<tr>
<td>4</td>
<td>13a</td>
<td>13b</td>
<td>13c</td>
</tr>
</tbody>
</table>

Scheme 4 Synthesis of diamagnetic and paramagnetic pyrrolo[3,4-b]pyrazine scaffolds and its CH functionalization
ethoxide to furnish compound 21. Its hydrolysis with NaOH to the carboxylic acid and the treatment of the crude product with 1,1'-carbonyldimidazole (CDI) in THF followed by treatment with aqueous 25% ammonia gave amide 22. Treatment of compound 22 with m-CPBA gave the spin-labeled analogue 23 of pyrazinamide in an 11% overall yield over four steps (Scheme 5).

![Scheme 5 Synthesis of paramagnetic pyrazinamide](image)

In order to extend the scope of utilization of compound 3, we tested it in a multicomponent Debrec-Radziszewski imidazole formation with modification of the Fallah and Mokhtary method utilizing tin oxide nanoparticles as catalysts. Therefore, compound 3, benzaldehyde (24), and ammonium acetate in the presence of SnO2 nanoparticles were heated at reflux temperature for 3 hours in EtOH. After the isolation of compound 25 in a 75% yield, we attempted the deprotection to nitroxide with m-CPBA, but the formation of (4,4,6,6-tetramethyl-2-phenyl-4,6-dihydropyrrolo[3,4-d]imidazol-5-yl)oxadanyl was not observed. Considering that Chalmers et al. reported a similar deprotection on N-substituted imidazole containing scaffolds, we decided on the protection of the imidazole NH by alkylation. Therefore, treatment of 25 with Mel in THF in the presence of NaH furnished compound 26, which can be deprotected to afford 1-methylimidazole-fused pyrroline nitroxide 27 in 44% yield in two steps (Scheme 6).

![Scheme 6 Synthesis of diamagnetic and paramagnetic 1-methyl-2-phenyl-4,6-dihydropyrrolo[3,4-d]imidazole scaffold](image)

In conclusion, we have developed access to 1-methoxy-2,2,5,5-tetramethylpyrroolidine-3,4-dione nitroxide precursor 3, which could be condensed with 1,2-diamines to give various quinoxalines, pyrazines, and pteridines fused with the pyrroline nitroxide precursor. The nitroxide functionality was restored by treatment of the NOME moiety with m-CPBA. Compound 3 also was used in 1-substituted imidazole-fused pyrroline nitroxide synthesis, as the m-CPBA deprotection cannot be conducted seemingly in the presence of the imidazole NH functional group.

We hope that compound 3, as a universal building block, can be used for the synthesis of further pyrroline nitroxide-fused structures. The evaluation of further possibilities as well as biological study of newly synthesized pyrazine derivatives are in progress in our laboratory.
2,2,5,5-Tetramethyl-1-trifluoroacetylpyrrolidin-3-one (5)
To a stirred solution of a mixture of 4 (1.2 g, 8.5 mmol) and Et3N (1.01 g, 10.0 mmol) in DCM (20 mL) was added (CF3CO)2O (2.1 g, 10.0 mmol) in DCM (5 mL) dropwise at 0 °C and the mixture was stirred at r.t. for 1 h. The mixture was washed with distilled H2O (20 mL) and the organic phase was separated. It was then dried (MgSO4), filtered, and evaporated to give 5 as a yellow oil; yield: 1.64 g (82%); Rf = 0.51 (hexane-EtOAc 2:1).

IR (neat): 2986, 2940, 1754 cm–1.

1H NMR (500 MHz, CDCl3): δ = 2.68 (s, 2 H, CH2), 1.64 (s, 6 H, 2 × CH3), 1.58 (s, 6 H, 2 × CH3).

13C NMR (125 MHz, CDCl3): δ = 211.4 (C=O), 157.0 (C=O, q, JCF3 = 38.3 Hz), 115.8 (CF3, q, JCF3 = 285.1 Hz), 99.9 (CH2), 61.94 (C), 50.76 (C), 27.54 (2 × CH3), 24.96 (2 × CH3).

MS (EI): m/z (%) = 237 (41, [M]+), 228 (48), 154 (50), 69 (91), 42 (100).


Oxidation of Compounds 2 and 5 with SeO2; General Procedure
To a solution of compound 2 or 5 (7.0 mmol) in glacial AcOH (10 mL) was added SeO2 (1.01 g, 10.0 mmol) in DCM (20 mL) was added (CF3CO)2O (2.1 g, 10.0 mmol) and the mixture was refluxed for 1 h. After cooling, the mixture was diluted with distilled H2O (10 mL), and filtered through a Celite pad. The pad was then washed with EtOAc (2 × 50 mL). The combined organic layers were dried (MgSO4), filtered, and evaporated to give 3 (from 2) as a brown oil; yield: 1.08 g (84%); Rf = 0.56 (hexane–EtOAc 2:1).

2-Methoxy-1,1,3,3-tetramethyl-2,3-dihydro-1H-pyrrolo[3,4-b]quinazoline (10b)
Yield: 900 mg (70%); white powder; mp 131–134 °C; Rf = 0.63 (hexane–EtOAc 2:1).

IR (neat): 3087, 3045, 2976, 1668 cm–1.

1H NMR (500 MHz, CDCl3): δ = 8.13 (dd, Jf = 7.0 Hz, Jf = 7.0 Hz, 2 H, ArH), 7.73 (dd, Jf = 7.0 Hz, Jf = 7.0 Hz, 2 H, ArH), 3.88 (s, 3 H, OCH3), 1.62 (s, 12 H, 4 × CH3).

13C NMR (125 MHz, CDCl3): δ = 160.2 (2 C), 142.9 (2 C), 129.1 (2 × CH2), 128.9 (2 × CH3), 65.8 (2 C), 65.7 (OCH3), 27.2 (2 × CH3), 23.2 (2 × CH3).

MS (EI): m/z (%) = 257 (31, [M]+), 242 (100), 196 (38), 42 (31).

Preparation of Compounds 7b, 8, 10b, and 11b; General Procedure
To a solution of compound 3 or 6 (5.0 mmol) in anhyd EtOH (20 mL) was added compound 7a, or 10a, or 11a (the latter was previously released from its 2 HCl salt with 2.0 equiv of NaOEt) (5.0 mmol) and the mixture was refluxed for 3 h and allowed to stay in air overnight. The solvent was evaporated and the residue was purified by flash column chromatography (hexane–EtOAc 2:1 or hexane–EtOAc 2:1, or CHCl3–EtO) to give compounds 7b or 8 or 10b or 11b.

1-Methoxy-2,2,5,5-tetramethylpyrrolidin-3,4-dione (3)
Yield: 1.38 g (86%); white powder; mp 166–168 °C; Rf = 0.60 (hexane–EtOAc 2:1).

IR (neat): 3027, 3011, 1658, 1501 cm–1.

1H NMR (500 MHz, CDCl3): δ = 8.17 (dd, Jf = 7 Hz, Jf = 7 Hz, 2 H, ArH), 7.82 (dd, Jf = 7 Hz, Jf = 7 Hz, 2 H, ArH), 1.97 (s, 12 H, 4 × CH3).

13C NMR (125 MHz, CDCl3): δ = 157.4 (2 C), 157.1 (C=O, q, JCF3 = 38 Hz), 143.4 (2 C), 129.0 (2 × CH2), 129.3 (2 × CH3), 119.4 (CF3, q, 285.2 Hz), 67.6 (2 C), 27.7 (4 × CH3).

MS (EI): m/z (%) = 323 (7, [M]+), 258 (50), 202 (28), 195 (70), 69 (26).

Anal. Calcd for C16H20N4O2: C, 63.98; H, 6.71; N, 18.65. Found: C, 62.94; H, 6.82; N, 12.86.

2-Methoxy-1,1,3,3-tetramethyl-2,3-dihydro-1H-pyrrolo[3,4-b]quinazolin-5-carboxamide (10b)
Yield: 414 mg (46%); white powder; mp 225–228 °C; Rf = 0.42 (CHCl3–EtOAc 2:1).

IR (neat): 3332, 3148, 2978, 2936 1618, 1576 cm–1.

1H NMR (500 MHz, DMSO-d6): δ = 9.24 (s, 1 H, NH), 8.49 (d, J = 7 Hz, 1 H), 8.29 (d, J = 8.5 Hz, 1 H, ArH), 7.95 (t, J = 8.5 Hz, 1 H, ArH), 3.82 (s, 3 H, OCH3), 1.55 (s, 12 H, 4 × CH3).

13C NMR (125 MHz, DMSO-d6): δ = 166.4 (C=O), 160.2 (C), 159.5 (C), 142.8 (C), 139.8 (C), 132.9 (2 × CH), 131.6 (CH), 129.6 (CH), 66.0 (2 C), 65.9 (OCH3), 28.0 (2 × CH2), 24.0 (2 × CH3).

MS (EI): m/z (%) = 300 (18, [M]+), 285 (100), 268 (10), 42 (13).


2,8-Dimethoxy-1,1,3,3,7,7,9,9-octamethyl-1,2,3,7,8,9-hexahydro-pyrrolo[3,4-b]pyrrole[3',4',5,6]pyrazino[2,3-g]quinoline (11b)
Yield: 588 mg (45%); beige powder; mp 246–250 °C; Rf = 0.51 (hexane–EtOAc 2:1).

IR (neat): 2977, 2918, 1636 cm–1.

1H NMR (500 MHz, CDCl3): δ = 8.86 (s, 2 H, ArH), 3.91 (s, 6 H, 2 × OCH3), 1.68 (s, 24 H, 8 × CH3).

13C NMR (125 MHz, CDCl3): δ = 162.3 (4 C), 141.3 (4 C), 128.5 (2 × CH2), 73.4 (2 C), 66.0 (4 C), 65.8 (2 × OCH3), 27.8 (4 × CH3), 22.6 (4 × CH3).

MS (EI): m/z (%) = 436 (21, [M]+), 421 (100), 375 (20), 329 (10), 43 (2).

7-Methoxy-6,6,8,8-tetramethyl-7,8-dihydro-6H-pyrrrolo[3,4-g]pteridine (12b)

To a solution of compound 3 (555 mg, 3.0 mmol) in glacial AcOH (10 mL) was added compound 12a (330 mg, 3.0 mmol) and the mixture was refluxed for 3 h. After cooling, the solvent was evaporated, and the residue was treated with distilled H2O (20 mL) and sat. aq K2CO3 (20 mL). The mixture was extracted with CHCl3 (3 × 30 mL), the combined organic phases were dried (MgSO4), filtered, and evaporated. The residue was purified by flash column chromatography (hexane–EtOAc, 1:1) to give compound 12b as a beige powder; yield: 385 mg (50%); mp 115–117 °C; Rf = 0.57 (CHCl3–EtOAc 2:1).

IR (neat): 3187, 3072, 2983, 1691, 1575, 1527 cm–1.


1H NMR (500 MHz, CDCl3): δ = 9.67 (s, 1 H, ArH), 9.51 (s, 1 H, ArH), 3.86 (s, 3 H, OCH3), 1.63 (s, 12 H, 4 × CH3).

13C NMR (125 MHz, CDCl3): δ = 169.2 (CH), 163.9 (CH), 162.4 (C), 158.0 (C), 154.6 (C), 134.6 (C), 66.4 (C), 66.0 (C), 65.8 (OCH3), 28.13 (2 × CH3), 23.02 (2 × CH3).

MS (EI): m/z (% = 291 (14, [M]+), 276 (100), 245 (23), 230 (23), 42 (23). (50%); mp 163–166 °C; Rf = 0.33 (CHCl3–MeOH 24:1).

13b

Preparation of 13b, 10c, 11c, 12c, 13c, 17, 23, and 27 by Deprotection of Methoxamines; General Procedure

Methoxamine 7b or 10b or 11b or 12b or 13b or 16b or 22b or 26b was stirred in DCM (20 mL) at r.t. Solid 3-chloroperbenzoic acid (~60%, 172 mg, 0.6 mmol in 2–3 portions at 0 °C over 10 min. The solution turned yellow-orange, and the stirring was continued for an additional 30 min at r.t. Then, the solution was washed with 10% aq Na2CO3 (2 × 10 mL), the organic phase was separated, dried (MgSO4), filtered, and evaporated. The residue was subjected to flash column chromatography (hexane–EtOAc 2:1) to afford compound 7c as a yellow powder; yield: 58 mg (48%); mp 168–170 °C; Rf = 0.41 (hexane–EtOAc, 2:1).

IR (neat): 3068, 2976, 2930, 1639, 1619, 1501 cm–1.

1H NMR [500 MHz, DMSO-d6 + (PhNH)2]: δ = 8.12 (dd, J = 7 Hz, J = 7 Hz, 2 H, ArH), 7.80 (dd, J = 7 Hz, J = 7 Hz, 2 H, ArH), 1.47 (s, 12 H, 4 × CH3).

13C NMR [125 MHz, CDCl3 + (PhNH)2]: δ = 160.9 (2 C), 142.6 (2 C), 129.3 (2 × CH), 129.2 (2 × CH), 65.2 (2 C), 55.2 (4 × CH3).

MS (EI): m/z (% = 242 (100, [M]+)), 211 (32), 197 (71), 42 (47).

Anal. Calcd for C14H17N3O: C, 73.98; H, 7.54; N, 18.49. Found: C, 73.81; H, 6.58; N, 17.17.

Preparation of 7c, 10c, 11c, 12c, 13c, 17, 23, and 27 by Deprotection of Methoxamines; General Procedure

Methoxamine 7b or 10b or 11b or 12b or 13b or 16b or 22b or 26b was stirred in DCM (20 mL) at r.t. Solid 3-chloroperbenzoic acid (~60%, 172 mg, 0.6 mmol in 2–3 portions at 0 °C over 10 min. The solution turned yellow-orange, and the stirring was continued for an additional 30 min at r.t. Then, the solution was washed with 10% aq Na2CO3 (2 × 10 mL), the organic phase was separated, dried (MgSO4), filtered, and evaporated. The residue was subjected to flash column chromatography (hexane–EtOAc 2:1) to afford compound 7c as a yellow powder; yield: 58 mg (48%); mp 168–170 °C; Rf = 0.41 (hexane–EtOAc, 2:1).
(1,3,3,7-Tetramethyl-2,3-dihydro-1H-pyrrolo[3,4-b]quinoxaline-5-carboxamide-2-yl)oxidanyl (10c)

Purified by flash column chromatography (hexane–EtOAc 2:1) to obtain an orange powder; yield: 348 mg (61%); mp 249–252 °C; Rf = 0.30 (CHCl₃–Et₂O 2:1).

IR (neat): 3357, 2984, 1672, 1575 cm⁻¹.

1H NMR (500 MHz, DMSO-d₆): δ = 9.42 (s, 1 H, NH₂), 8.56 (dd, J = 7.5 Hz, 1 H, ArH), 8.29 (dd, J = 8 Hz, 1 H, ArH), 8.01 (m, 2 H, ArH and NH₂). 1.48 (s, 12 H, 4 × CH₃).

13C NMR (125 MHz, DMSO-d₆): δ = 166.4 (C=O), 161.0 (C), 160.3 (C), 142.7 (C), 139.3 (C), 133.0 (C), 132.3 (CH), 131.2 (CH), 129.3 (CH), 65.3 (2 C), 25.2 (2 × CH₃), 25.1 (2 × CH₃).

MS (El): m/z (%) = 285 (100, [M⁺]), 255 (12), 238 (48), 42 (20).


(5,5,7,7-Tetramethyl-7H-pyrrolo[3,4-b]pyrazin-6-yl)oxidanyl (17)

Yield: 300 mg (78%); yellow powder; mp 118–121 °C; Rf = 0.43 (hexane–EtOAc 2:1).

IR (neat): 2973, 2929, 1541 cm⁻¹.

1H NMR [500 MHz, DMSO-d₆ + (PhNH)₂]: δ = 8.47 (s, 2 H, ArH), 1.36 (s, 12 H, 4 × CH₃).

13C NMR [125 MHz, DMSO-d₆ + (PhNH)₂]: δ = 159.0 (2 C), 144.2 (2 × CH), 65.3 (2 C), 25.3 (4 C).

MS (El): m/z (%) = 192 ([M⁺], 50) 162 (41), 147 (100), 132 (30), 42 (37).


(5,5,7,7-Tetramethyl-6,7-dihydro-7H-pyrrolo[3,4-b]pyrazine-2-carboxamide-6-yl)oxidanyl (23)

Purified by flash column chromatography (CHCl₃–EtOAc 2:1) to afford a yellow powder; yield: 90 mg (65%); mp 220–223 °C; Rf = 0.51 (CHCl₃–MeOH 24:1).

IR (neat): 3475, 3268, 2981, 1692, 1572 cm⁻¹.

1H NMR [500 MHz, DMSO-d₆ + (PhNH)₂]: δ = 9.08 (s, 1 H, ArH), 1.41 (s, 6 H, 2 × CH₃). 1.39 (s, 6 H, 2 × CH₃).

13C NMR [125 MHz, DMSO-d₆ + (PhNH)₂]: δ = 165.6 (C=O), 161.9 (C), 157.7 (C), 145.0 (C), 143.1 (CH), 65.5 (C), 65.2 (C), 25.8 (4 × CH₃).

MS (El): m/z (%) = 235 (57, [M⁺], 205 (34), 190 (44), 42 (100).

Anal. Calc. for C₂₄H₂₂N₅O₂: C, 56.16; H, 6.43; N, 23.81. Found: C, 56.24; H, 6.18; N, 23.76.

(1,4,4,6,6-Pentamethyl-2-phenyl-4,6-dihydroxy-1H-pyrrolo[3,4-dimiazol-5-yl]oxidanyl (27)

Purified by flash column chromatography (hexane–EtOAc 2:1) to afford yellow crystals; yield: 350 mg (65%); mp 133–135 °C; Rf = 0.47 (CHCl₃–Et₂O 2:1).

IR (neat): 2973, 2927, 1577 cm⁻¹.

1H NMR [500 MHz, CDCl₃ + (PhNH)₂]: δ = 7.69 (d, J = 7.5 Hz, 2 H, ArH), 7.47–7.44 (m, 1 H, ArH), [2 aromatic H overlapped with (PhNH)₂ signals], 3.69 (s, 3 H, NCH₃), 1.59 (s, 6 H, 2 × CH₃), 1.58 (s, 6 H, 2 × CH₃).

13C NMR [125 MHz, CDCl₃ + (PhNH)₂]: δ = 150.2 (C), 148.9 (C), 145.8 (C), 134.8 (C), 130.7 (CH), 129.0 (2 × CH), 128.5 (2 × CH), 64.7 (C), 64.1 (C), 32.4 (NCH₃), 25.4 (2 × CH₃), 25.2 (2 × CH₃).

MS (El): m/z (%) = 270 (2, [M⁺], 240 (100), 225 (89), 211 (20), 77 (15), 43 (16).

Anal. Calc. for C₂₂H₂₁N₅O₂: C, 71.08; H, 7.46; N, 15.54. Found: C, 71.02; H, 7.35; N, 15.67.

6-Methoxy-5,5,7,7-tetramethyl-3,5,6,7-tetrahydro-2H-pyrrolo[3,4-b]pyrazine (15)

A solution of compound 3 (740 mg, 4.0 mmol) and 1,2-diaminoethane (240 mg, 4.0 mmol) in anhyd EtOH (20 mL) was refluxed for 1 h under N₂ and then left to stand overnight. The solvent was evaporated, and the residue was purified by flash column chromatography (hexane–EtOAc 2:1) to afford a colorless oil; yield: 593 mg (71%); Rf = 0.33 (CHCl₃–Et₂O 2:1).

IR (neat): 2978, 2940, 2900, 1641 cm⁻¹.
To a stirred solution of compound 15 (418 mg, 2.0 mmol) in anhyd MeOH (10 mL) was added a solution of NaOEt [freshly prepared from Na (92 mg, 4.0 mmol) and anhyd EtOH (20 mL)] and then, the resulting mixture was refluxed for 4 h under N2. After cooling, the solvents were evaporated, and the residue was partitioned between sat. aq NH₄Cl (20 mL) and CHCl₃ (50 mL). The organic phase was separated, dried (MgSO₄), filtered, and evaporated. The residue was purified by flash column chromatography (hexane–EtOAc 2:1) to give compound 16 as a colorless oil: yield: 223 mg (54%); Rₖ = 0.56 (hexane–EtOAc 2:1).

IR (neat): 3060, 2978, 2932, 1585 cm⁻¹.

1H NMR [500 MHz, CDCl₃ + (PhNH)₂]: δ = 3.73 (s, 3 H, OCH₃), 3.54 (s, 4 H, 2 × CH₂), 1.34 (s, 12 H, 2 × CH₃).

13C NMR [125 MHz, CDCl₃ + (PhNH)₂]: δ = 166.8 (2 C), 65.6 (OCH₃), 64.3 (2 C), 44.9 (2 × CH₂), 27.0 (2 × CH₃), 21.0 (2 × CH₃).

MS (EI): m/z (%) = 209 (31, [M]+), 194 (100), 162 (62), 42 (34).


Ethyl 6-Methoxy-5,5,7,7-tetramethyl-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazine-2-carboxylate (21)

To a stirred suspension of compound 20 HCl salt (1.03 g, 5.0 mmol) in EtOH (30 mL) was added freshly prepared NaOEt [from Na (230 mg, 10.0 mmol) and anhyd EtOH (20 mL)]. The precipitated NaCl was filtered out, and to the filtrate compound 3 (925 mg, 5.0 mmol) was added in one portion, followed by heating at reflux temperature for 1 h under N₂. A second portion of NaOEt (prepared from Na (230 mg, 10.0 mmol) and anhyd EtOH (20 mL)) was added, and the reaction mixture was refluxed for 4 h under N₂. After standing overnight at r.t. in air, solvents were evaporated, and the residue was partitioned between sat. aq NH₄Cl (20 mL) and CHCl₃ (50 mL). The organic phase was separated, dried (MgSO₄), filtered, and evaporated. The residue was purified by flash column chromatography (hexane–EtOAc 2:1) to give compound 21 as a yellow oil: yield: 502 mg (36%); Rₖ = 0.55 (hexane–EtOAc 2:1).

IR (neat): 2979, 2936, 1720, 1573, 1559 cm⁻¹.

1H NMR [500 MHz, CDCl₃]: δ = 9.09 (s, 1 H, ArH), 4.52 (q, J = 7.5 Hz, 2 H, OCH₂CH₃), 3.81 (s, 3 H, OCH₃), 1.55 (s, 12 H, 4 × CH₃), 1.46 (1.5 Hz, 3 H, 3 H, OCH₂CH₃).

13C NMR [125 MHz, CDCl₃]: δ = 164.4 (C=O), 162.3 (C), 158.9 (C), 145.4 (CH), 143.0 (C), 66.0 (2 C), 65.7 (OCH₃), 62.0 (OCH₂), 28.0 (2 × CH₃), 22.9 (2 × CH₃), 14.3 (CH₃).

MS (EI): m/z (%) = 279 (12, [M]+), 264 (100), 218 (6).


6-Methoxy-5,5,7,7-tetramethyl-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazine-2-carboxamide (22)

To a solution of compound 21 (558 mg, 2.0 mmol) in EtOH (20 mL) was added eq 10% NaOH (2 mL) and the mixture was heated for 1 h. After standing overnight at r.t., the EtOH was evaporated off. The residue was dissolved in anhyd THF (25 mL), and carbonyl diimidazole (CDI, 405 mg, 2.5 mmol) was added to the resulting solution. The mixture was heated for 15 min, and then 25% eq NH₄OH solution (5 mL) was added, followed by an additional 10 min of heating. After cooling, the mixture was extracted with CHCl₃ (2 × 30 mL). The combined organic phases were dried (MgSO₄), filtered, and evaporated. The residue was heated for 15 min, and then 25% eq NH₄OH solution (5 mL) was added, followed by an additional 10 min of heating. After cooling, the mixture was extracted with CHCl₃ (2 × 30 mL). The combined organic phases were dried (MgSO₄), filtered, and evaporated. The residue was purified by flash column chromatography (hexane–EtOAc 2:1) to give compound 22 as a yellow oil; yield: 405 mg (36%); Rₖ = 0.33 (hexane–EtOAc 2:1).

IR (neat): 3060, 2978, 2932, 1585 cm⁻¹.

1H NMR [500 MHz, CDCl₃ + (PhNH)₂]: δ = 8.55 (s, 1 H, ArH), 7.87 (d, J = 9.5 Hz, 2 H, ArH), [3 aromatic H overlapped with (PhNH)₂ signals], 1.78 (s, 6 H, 2 × CH₃), 1.63 (s, 6 H, 2 × CH₃).

13C NMR [125 MHz, CDCl₃ + (PhNH)₂]: δ = 161.4 (C), 147.0 (CH), 144.3 (C), 144.1 (C), 130.1 (CH), 129.5 (2 × CH), 129.3 (C), 128.6 (2 × CH), 67.1 (C), 66.6 (C), 24.8 (2 × CH₂), 22.0 (2 × CH₃).

MS (EI): m/z (%) = 284 (14, [M]+), 254 (52), 239 (100), 195 (77), 75 (57), 42 (85).

purified by flash column chromatography (hexane–EtOAc, 2:1) to give compound 22 as a beige solid; yield: 247 mg (66%); mp 158–160 °C; \( R_f = 0.36 \) (CHCl\(_3\)–EtOAc 2:1).

IR (neat): 3440, 3197, 2977, 2948, 1685, 1575 cm\(^{-1}\).

\( ^1\)H NMR (500 MHz, DMSO-\( d_6 \)); \( \delta = 9.03 \) (s, 1 H, NH\(_2\)), 8.18 (s, 1 H, NH\(_2\)), 7.84 (s, 1 H, ArH), 3.77 (s, 3 H, OCH\(_3\)), 1.45 (s, 12 H, 4 × CH\(_3\)).

\( ^{13}\)C NMR (125 MHz, CDCl\(_3\)); \( \delta = 165.4 \) (C=O), 160.9 (C), 156.8 (C), 145.3 (CH\(_3\)), 143.4 (C), 66.1 (C), 65.8 (C), 65.7 (OCH\(_3\)), 27.7 (2 × CH\(_3\)), 23.3 (2 × CH\(_3\)).

MS (EI): \( m/z \) (\%) = 250 (14, [M]+), 235 (100), 189 (20), 42 (43).

Anal. Calcd for C\(_{16}\)H\(_{21}\)N\(_3\)O: C, 70.82; H, 7.80; N, 15.49. Found: C, 70.75; H, 7.20; N, 15.64.

**5-Methoxy-2-phenyl-4,4,6,6-tetramethyl-1,4,5,6-tetrahydro-
pyrrolo[3,4-d]imidazole (25)**

To a stirred solution of compound 3 (740 mg, 4.0 mmol) in anhyd EtOH (20 mL) were added NH\(_4\)OAc (616 mg, 8.0 mmol), SnO\(_2\) (s, 12 H, 4 × CH\(_3\)). 1H NMR (500 MHz, CDCl\(_3\) + (PhNH)\(_2\)):

\( \delta = 7.95 \) (d, \( J = 7 \) Hz, 2 H, ArH), 7.35–7.29 (m, 3 H, ArH), 3.75 (s, 3 H, OCH\(_3\)), 1.39 (s, 12 H, 4 × CH\(_3\)).

\( ^{13}\)C NMR (125 MHz, CDCl\(_3\)); \( \delta = 148.7 \) (C), 140.0 (C), 130.2 (C), 128.8 (2 × CH), 128.6 (CH), 125.3 (2 × CH), 65.6 (OCH\(_3\)), 64.2 (C), 30.92 (4 × CH\(_3\)).

MS (EI); \( m/z \) (\%) = 271 (8, [M]+), 256 (42), 227 (43), 43 (100).

Anal. Calcd for C\(_{25}\)H\(_{27}\)N\(_2\)O: C, 70.82; H, 7.80; N, 15.49. Found: C, 70.75; H, 7.20; N, 15.64.

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**Supporting Information**

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690678.

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