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

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Dedicated to the memory of Prof. Kálmán Hideg

Abstract 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-tetramethylpyrrolidine-3,4-dione by SeO2 oxidation of 1-oxyl-2,2,5,5-tetramethylpyrrolidine-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]quinolines 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 trifluoroacetamido 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-diaminobenzamide (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).
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-diaminopropanoic acid HCl salt 20 in EtOH with 4.0 equivalents of sodium

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>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10a</td>
<td>10b</td>
<td>10c</td>
</tr>
<tr>
<td>2</td>
<td>11a</td>
<td>11b</td>
<td>11c</td>
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<tr>
<td>3</td>
<td>12a</td>
<td>12b</td>
<td>12c</td>
</tr>
<tr>
<td>4</td>
<td>13a</td>
<td>13b</td>
<td>13c</td>
</tr>
</tbody>
</table>

* Reflux in AcOH.
* Reflux in MeOH–H2O.

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).

In order to extend the scope of utilization of compound 3, we tested it in a multicomponent Debos–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)oxidanyl 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).

In conclusion, we have developed access to 1-methoxy-2,2,5,5-tetramethylpyrrolidine-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 NMe 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.

Melting points were determined with a Boetius micro-melting point apparatus and are uncorrected. Elemental analyses (C, H, N, and S) were performed with a Fisons EA 1110 CHNS elemental analyzer. Mass spectra were recorded on a ThermoQuest autosam Multispectrometer. NMR spectra were recorded on a Bruker Avance III 500 spectrometer; chemical shifts are referenced to TMS. The paramagnetic compounds were reduced to N-hydroxylamines with five equivalents of hydrazobenzene (DPPH)/radicals in situ in the NMR tube. Measurements were performed at a probe temperature 298 K in CDCl3 or DMSO-d6 or CD3OD solution. ESR spectra were recorded on a Miniscope MS 200 in CHCl3 solution. All monoradicals gave a triplet line at $a_H = 14.5$ G. Biradical 11c gave a quartet line at $a_H = 7.3$ G. IR spectra were recorded with a Bruker Alpha FT-IR instrument with ATR support (ZnSe plate). Flash column chromatography was performed on Merck Kieselgel 60 (230–400 mesh). Compounds 14, 21, 23, and 27 were prepared as described previously. Compounds 7a, 10a–13a, 14, 24 and other reagents were purchased from Merck, Alfa Aesar, and TCI.

1-Methoxy-2,2,5,5-tetramethylpyrrolidin-3-one (2)

To a stirred solution of 1 (1.56 g, 10.0 mmol) and FeSO4·H2O (6.9 g, 25.0 mmol) in DMSO (50 mL) at 0 °C was added 30% aq H2O2 (5 mL) dropwise over 2 h. The reaction was monitored by TLC. Upon consumption of the starting material, distilled H2O (50 mL) was added and the aqueous solution was extracted with Et2O (3 × 30 mL). The combined organic phases were dried (MgSO4), filtered, and evaporated, and the crude product was purified by flash column chromatography (hexane–EtOAc, 2:1) to give 2 as a colorless oil; yield: 1.28 g (75%); $R_f = 0.58$ (hexane–EtOAc 2:1).

IR (neat): 2972, 2940, 1751 cm$^{-1}$

$^1$H NMR (500 MHz, CDCl3): $\delta = 3.72$ (s, 3 H, OCH3), 2.34 (s, 2 H, CH2), 1.29 (s, 6 H, 2 × CH3), 1.26 (s, 6 H, 2 × CH3).

$^{13}$C NMR (125 MHz, CDCl3): $\delta = 216.3$ (C=O), 67.2 (C), 65.2 (CH2), 61.2 (OCH3), 49.76 (C), 31.59 (2 × CH3), 22.65 (2 × CH3).

MS (EI): $m/z = 171$ (3, [M]+), 156 (25), 70 (48), 42 (100).
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 Et2N (10.1 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. After cooling, the mixture was diluted with distilled H2O (10 mL), washed with EtOAc (2 × 50 mL). The combined organic layers were dried (MgSO4), filtered, and evaporated to give 5 as a yellow oil; yield: 1.08 g (84%).

1H NMR (500 MHz, CDCl3): δ = 2.52 (2 × CH3), 2.40 (2 × CH3), 1.39 (s, 12 H, 4 × CH3).

13C NMR (125 MHz, CDCl3): δ = 211.4 (C), 157.0 (C=O, q, 2 JCF = 38.3 Hz), 115.8 (CF3, q, 1 JCF = 285.1 Hz), 99.9 (CH2), 61.9 (C), 50.7 (C), 27.4 (2 × CH3), 24.9 (2 × CH3).

IR (neat): 2986, 2940, 1754 cm–1.

13C NMR (125 MHz, DMSO-d6): δ = 206.2 (2 × C=O), 67.3 (2 C), 65.7 (OCH3), 25.3 (2 × CH3), 19.7 (2 × CH3).

To a solution of compound 4 (1.01 g, 10.0 mmol) in DCM (20 mL) was added SeO2 (1.16 g, 10.5 mmol) and the mixture was refluxed 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, and the crude product was purified by flash column chromatography (hexane–Et2O, 2:1) to give 6 as a yellow oil; yield: 1.08 g (84%).

1H NMR (500 MHz, CDCl3): δ = 3.76 (s, 3 H, OCH3), 1.39 (s, 12 H, 4 × CH3).

13C NMR (125 MHz, CDCl3): δ = 202.6 (2 × C=O), 66.0 (4 C), 65.8 (2 × OCH3), 65.7 (OCH3), 27.2 (2 × CH3), 23.2 (2 × CH3).

MS (EI): m/z (%): 323 (7, [M]+), 308 (100), 195 (70), 69 (26).

Ana 1-Methoxy-2,2,5,5-tetramethylpyrrolidin-3,4-dione (3)

Both crude diketo compounds 3 and 6 were used immediately in the next step. Purification of the crude products were attempted by flash chromatography (hexane–EtOAc 2:1) for analysis only, however, compound 6 proved to be unstable.

1-Methoxy-2,2,5,5-tetramethylpyrrolidin-3,4-dione (3)

Yellow crystals; mp 41–42 °C; Rf = 0.51 (hexane–EtOAc 2:1); visualization by I2 vapor.

IR (neat): 2986, 2940, 1754 cm–1.

1H NMR (500 MHz, CDCl3): δ = 3.76 (s, 3 H, OCH3), 1.39 (s, 12 H, 4 × CH3).

13C NMR (125 MHz, CDCl3): δ = 202.6 (2 × C=O), 67.3 (2 C), 65.7 (OCH3), 25.3 (2 × CH3), 19.7 (2 × CH3).

MS (EI): m/z (%): 186 (33, [M]+), 185 (7), 144 (23), 98 (100), 88 (60), 43 (27).

Anal. Calcld for C8H14NO2: C, 63.98; H, 6.71; N, 18.65. Found: C, 63.98; H, 6.82; N, 18.58.

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–EtO 2:1 or hexane–EtOAc 2:1, or CHCl3–EtO) to give compounds 7b or 8 or 10b or 11b.

2-Methoxy-1,1,3,3-tetramethyl-2,3-dihydro-1H-pyrrolo[3,4-b]quinazoline (7b)

Yield: 900 mg (70%); white powder; mp 131–134 °C; Rf = 0.63 (hexane–EtO 2:1).

IR (neat): 3078, 3045, 2976, 1688 cm–1.

1H NMR (500 MHz, CDCl3): δ = 8.83 (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 = 162.0 (2 C), 142.9 (2 C), 129.1 (2 × CH), 128.9 (2 × CH), 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).

Anal. Calcld for C16H20N4O2: C, 63.98; H, 6.71; N, 18.65. Found: C, 63.98; H, 6.82; N, 18.58.
7-Methoxy-6,6,8,8-tetramethyl-7,8-dihydro-6H-pyrrolo[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–Et2O 2:1).

IR (neat): 3064, 2976, 2930, 1639, 1619, 1501 cm–1.

1H NMR (500 MHz, CDCl3): δ = 9.73 (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 = 168.9 (2 C), 163.9 (CH), 162.4 (C), 158.0 (C), 154.5 (CH3CO), 146.4 (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 (%): 259 (14, [M]+), 244 (100), 213 (33), 198 (22), 42 (8).

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

Methoxyamine 7b or 10b or 11b or 12b or 13b or 16 or 22 or 26 (2.0 mmol) was stirred in DCM (20 mL) at r.t. Solid 3-chloroperbenzoic acid (–60%, 172 mg, 0.6 mmol) was stirred in DCM (20 mL) at r.t. Solid 3-chloroperbenzoic acid (~60%, 1.43 g, 5.0 mmol and 2.86 g 10.0 mmol for 11b) was added portionwise over a period of 10 min. The reaction was monitored by TLC and upon the consumption of the starting material (~24 h), as monitored by TLC. After cooling, the solution was washed with 10% aq Na2CO3 (2 × 10 mL), 10% aq NaOH (2 × 10 mL), and then H2O (10 mL). The organic phase was separated, dried (MgSO4), filtered, and evaporated. The residue was purified by flash column chromatography (hexane–EtOAc 1:1, then CHCl3–Et2O 2:1) to afford compound 7c as a yellow powder; yield: 58 mg (48%); mp 168–170 °C; Rf = 0.41 (hexane–EtO, 2:1).

IR (neat): 3064, 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 C14H17N3: C, 73.98; H, 7.54; N, 18.49. Found: C, 73.81; H, 6.60; N, 17.29.
Purified by flash column chromatography (hexane–EtOAc 2:1) to obtain an orange powder; yield: 348 mg (61%); mp 249–252 °C; \( R_f = 0.30 \) (CHCl₃–Et₂O 2:1).

IR (neat): 3357, 3180, 2984, 1672, 1575 cm⁻¹.

¹H NMR (500 MHz, DMSO-\( d_6 \)) d = 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-\( d_6 \)): \( \delta = 166.4 \) (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 (C), 25.2 (2 × CH₃), 25.1 (2 × CH₃).

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


Purified by flash column chromatography (hexane–EtOAc 2:1) to afford a brown powder; yield: 422 mg (52%); mp 235–238 °C; \( R_f = 0.44 \) (CHCl₃–Et₂O 2:1).

IR (neat): 2990, 2933, 1548 cm⁻¹.

¹H NMR and ¹³C NMR spectra cannot be recorded because of precipitation of compound 11c in DMSO-d₆ in the presence of 10.0 equiv of (PhNH₂). For an EPR spectrum, see SI.

MS (EI): m/z (%) = 406 (100, [M⁺]), 391 (63), 361 (48), 346 (43), 331 (27), 158 (29).


Purified by flash column chromatography (hexane–EtOAc 2:1) to afford a brown powder; yield: 317 mg (65%); mp 202–205 °C; \( R_f = 0.41 \) (CHCl₃–Et₂O 2:1).

IR (neat): 3063, 3023, 2979, 2931, 1615, 1572, 1556 cm⁻¹.

¹H NMR [500 MHz, CDCl₃ + (PhNH₂)]: \( \delta = 9.84 \) (s, 1 H, ArH), 9.60 (s, 1 H, ArH), 1.71 (s, 6 H, 2 × CH₃), 1.67 (s, 6 H, 2 × CH₃).

¹³C NMR [125 MHz, CDCl₃ + (PhNH₂)]: \( \delta = 169.2 \) (CH), 163.9 (CH), 162.3 (C), 158.0 (C), 154.7 (C), 143.70 (C), 136.6 (C), 66.5 (C), 66.1 (C), 24.9 (2 × CH₃), 24.8 (2 × CH₃).

MS (EI): m/z (%) = 244 (77, [M⁺]), 214 (28), 213 (33), 199 (100), 184 (38).


Purified by flash column chromatography (hexane–EtOAc 2:1) to afford a bordeaux colored powder; yield: 300 mg (65%); mp 220–223 °C; \( R_f = 0.51 \) (CHCl₃–MeOH 24:1).

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

¹H NMR [500 MHz, DMSO-d₆ + (PhNH₂)]: \( \delta = 9.08 \) (s, 1 H, ArH), 1.41 (s, 6 H, 2 × CH₃), 1.39 (s, 6 H, 2 × CH₃).

¹³C NMR [125 MHz, DMSO-d₆ + (PhNH₂)]: \( \delta = 165.6 \) (C=O), 161.9 (C), 157.7 (C), 145.0 (C), 143.1 (CH), 165.5 (C), 65.2 (C), 25.8 (4 × CH₃).

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

Anal. Calcd for C₁₂H₁₄N₅O₃: C, 56.16; H, 6.43; N, 23.81. Found: C, 56.24; H, 6.18; N, 23.76.

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

IR (neat): 2973, 2927, 1577 cm⁻¹.

¹H NMR [500 MHz, CDCl₃ + (PhNH₂)]: \( \delta = 7.69 \) (d, \( J = 7.5 \) Hz, 2 H, ArH), 7.47–7.44 (m, 1 H, ArH), 2 aromatic H overlapped with (PhNH₂) 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 + (PhNH₂)]: \( \delta = 150.2 \) (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 × CH₂), 25.2 (2 × CH₂).

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

Anal. Calcd for C₁₅H₁₅N₄O₂: C, 71.08; H, 7.46; N, 15.54. Found: C, 71.02; H, 7.35; N, 15.67.

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%); \( R_f = 0.33 \) (CHCl₃–Et₂O 2:1).

IR (neat): 2978, 2940, 2900, 1641 cm⁻¹.
Synthesis

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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, 4 × CH3).

13C NMR [125 MHz, CDCl3 + (PhNH)2]: δ = 147.0 (C), 143.1 (C), 134.5 (CH), 69.0 (C), 66.8 (C), 61.4 (C), 24.1 (2 × CH2), 21.3 (2 × CH3).

MS (EI): m/z (%) = 208 (16, [M]+), 178 (64), 161 (100), 154 (52), 137 (32), 105 (33), 31 (100). Anal. Calcd for C11H17N3O: C, 63.74; H, 8.27; N, 20.27. Found: C, 63.65; H, 8.18; N, 20.10.

(1-Oxyl-2-phenyl-5,5,7,7-tetramethyl-5,6-dihydro-5H-pyrrolo[3,4-b]pyrazin-6-yl)oxidanyl (18)

A degassed mixture of Pd(OAc)2 (22.0 mg, 0.1 mmol), Ag2CO3 (605 mg, 2.2 mmol), and compound 18 (208 mg, 1.0 mmol) in benzene (5 mL) in a screw-capped vial was stirred at 130 °C for 16 h in an oil bath. After cooling, the mixture was filtered through a plug of Celite, and then washed with EtOAc (40 mL). The solvents were evaporated and the residue was purified by flash column chromatography (hexane–EtOAc 2:1) to give compound 19 as yellow crystals; yield: 502 mg (36%); IR (neat): 3036, 2980, 2934, 1545 cm–1. Rf = 0.55 (hexane–EtOAc 2:1).

IR (neat): 3086, 2979, 2968, 1691, 1588 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 (1.7 Hz, 3 H, 3 × 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 × CH2), 14.3 (CH3).

MS (EI): m/z (%) = 279 (12, [M]+), 264 (100), 218 (6). Anal. Calcd for C33H32N2O4: C, 60.26; H, 7.49; N, 14.96.

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

To a stirred suspension of compound 20 (856 mg, 5.0 mmol) in EtOH (10 mL) was added freshly prepared NaOEt [prepared 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 chromatography (hexane–EtOAc 2:1) to give compound 21 as a yellow oil; yield: 502 mg (36%); IR (neat): 3049, 2980, 2934, 1545 cm–1. Rf = 0.55 (hexane–EtOAc 2:1).

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

1H NMR [500 MHz, CDCl3]: 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]: δ = 161.4 (C), 147.0 (CH), 144.3 (CH), 141.1 (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 (75), 77 (57), 42 (85). Anal. Calcd for C11H19N3O: C, 67.8; H, 6.43; N, 14.08.

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5-Methoxy-2-phenyl-1,4,4,6,6-pentamethyl-1,4,5,6-tetrahydro-pyrrrolo[3,4-d]imidazole (25)

To a stirred solution of compound 3 (740 mg, 4.0 mmol) in anhyd EtOH (20 mL) were added NH₄OAc (616 mg, 8.0 mmol), SnO₂ (s, 12 H, 4 × CH₃). The mixture was refluxed for 3 h, and after cooling, the mixture was filtered through plug of Celite, followed by evaporation of the filtrate. The residue was partitioned between DCM (50 mL) and distilled H₂O (30 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 25 as a white powder; yield: 813 mg (75%); mp 250–253 °C; Rᵢ = 0.42 (hexane–EtOAc 2:1).

IR (neat): 3055, 3032, 2971, 1600 cm⁻¹.

1H NMR (500 MHz, CDCl₃): δ = 7.95 (d, J = 7 Hz, 2 H, ArH), 7.35–7.29 (m, 3 H, ArH), 3.75 (s, 3 H, OCH₃), 1.39 (s, 12 H, 4 × CH₃).

13C NMR (125 MHz, CDCl₃): δ = 148.7 (C), 140.0 (C), 130.2 (C), 128.8 (2 × CH), 128.6 (CH), 125.3 (2 × CH), 65.6 (OCH₃), 64.2 (2 C), 30.92 (4 × CH₃).

IR (neat): m/z (%) = 271 (8, [M⁺]), 256 (42), 227 (43), 43 (100).

Anal. Calc'd for C₁₆H₂₁N₃O: C, 70.82; H, 7.80; N, 15.49. Found: C, 70.75; H, 7.20; N, 15.64.

5-Methoxy-1,4,4,6,6-pentamethyl-2-phenyl-1,4,5,6-tetrahydropyrrrolo[3,4-d]imidazole (26)

To a stirred suspension of NaH (48 mg, 2.0 mmol) in anhyd THF (10 mL) was added a solution of compound 25 (542 mg, 2.0 mmol) in THF (20 mL) dropwise at 0 °C under N₂. After 30 min, Mel (426 mg, 3.0 mmol) was added dropwise at 0 °C. After stirring the mixture for 3 h at r.t., the solvent was evaporated, and the residue was partitioned between EtOAc (40 mL) and distilled H₂O (20 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 26 as a white solid; yield: 387 mg (68%); mp 158–160 °C; Rᵢ = 165.4 (C=O), 160.9 (C), 156.8 (C), 145.3 (CH), 143.4 (C), 66.1 (C), 65.8 (OCH₃), 65.7 (OCH₃), 27.7 (2 × CH₂), 23.3 (2 × CH₃).

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


Funding Information

Financial supports from Hungarian National, Research, Development and Innovation Office (OTKA 124331) and grant GINOP (GINOP-2.3.2-15-2016-00049) are greatly acknowledged.

Acknowledgment

M.I. thanks the Stipendium Hungaricum Scholarship.

Supporting Information

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

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