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SHORT COMMUNICATIONS

Synthesis of 1-Alkoxy-4-amino-3,6-dioxo-1-phenyl-2,3,5,6-tetrahydro-1*H*-pyrrolo[3,4-*c*]pyridine-7-carbonitriles

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Abstract—1-Alkoxy-4-amino-3,6-dioxo-1-phenyl-2,3,5,6-tetrahydro-1*H*-pyrrolo[3,4-*c*]pyridine-7-carbonitriles have been synthesized with high yields by reaction of 4-amino-1-hydroxy-3,6-dioxo-1-phenyl-2,3,5,6-tetrahydro-1*H*-pyrrolo[3,4-*c*]pyridine-7-carbonitrile with the corresponding alcohols in the presence of *p*-toluenesulfonic acid.

Keywords: pyridine, alcohol, pyrrolo[3,4-*c*]pyridine, hemiaminal

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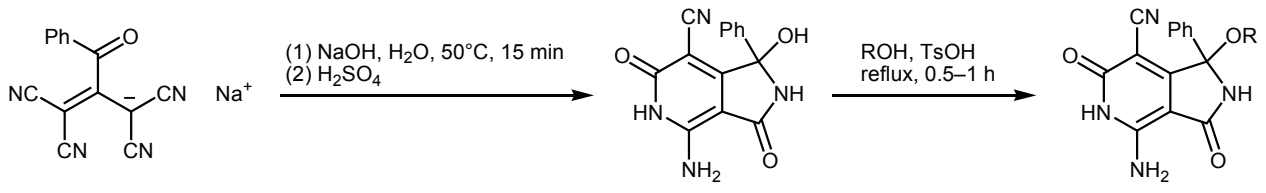
Derivatives of isoindolin-3-one and 5-azaisoindolin-3-one exhibit various biological activities and are therefore studied as drug candidates. For example, inhibitors of SYK (antitumor activity) [1], MDM2 (apoptotic activity) [2], and InhA (antitubercular activity) [3] have been found among these series of compounds. We previously showed that sodium tetracyanopropenides **1** are convenient precursors to polyfunctionalized pyrrolo[3,4-*c*]pyridines possessing a hemiaminal fragment [4–6]. With the aim of further modifying the latter, we examined the possibility of replacing the hemiaminal hydroxy group by alkoxy. This replacement may be useful to enhance their lipophilicity. According to published data, dehydroxylation/alkoxylation of such systems was accomplished using I_2 [7], $SOCl_2$ [3], MsCl in the presence of triethylamie [8], HCl [9], and camphorsulfonic acid [10]. We used as starting compound 4-amino-1-hydroxy-3,6-dioxo-1-phenyl-2,3,5,6-tetrahydro-1*H*-pyrrolo[3,4-*c*]pyridine-7-carbonitrile (**2**) which was synthesized by treatment of **1** with sodium hydroxide [4]. Compound **2** was reacted with alcohols in the presence of sulfuric acid or *p*-toluenesulfonic acid; the alcohol simultaneously acted as a solvent. When an equimolar amount of the acid was used, the reactions under reflux conditions were complete in 0.5–1 h. 1-Alkoxy-4-amino-3,6-dioxo-1-phenyl-2,3,5,6-tetrahydro-1*H*-pyrrolo[3,4-*c*]pyridine-7-carbonitriles **3a**–**3f** were isolated in 53–77% yield (Scheme 1), and their structure was confirmed by IR, ^{1}H and ^{13}C NMR, and mass spectra.

4-Amino-1-methoxy-3,6-dioxo-1-phenyl-2,3,5,6-tetrahydro-1*H*-pyrrolo[3,4-*c*]pyridine-7-carbonitrile (3a). A mixture of 0.564 g (0.002 mol) of compound **2**, 5 mL of methanol, and 0.034 g (0.0002 mol) of *p*-toluenesulfonic acid was refluxed until the reaction was complete (TLC, AcOEt–EtOH 9:1). The solvent was distilled off, and the residue was crystallized

Scheme 1.



1 **2** **3a–3f**

R=Me (**a**), Et (**b**), Pr (**c**), *i*-Pr (**d**), Bu (**e**), *i*-Bu (**f**).

from aqueous acetonitrile. Yield 0.456 g (77%), white powder, mp 207–209°C (decomp.). IR spectrum, ν, cm^{-1}: 3401, 3301, 3182, 3164 (NH, NH_2), 2222 (C≡N), 1692, 1638 (C=O). ^1H NMR spectrum, δ, ppm: 3.22 s (3H, CH_3), 7.30–7.70 m (7H, H_{arom}, NH_2), 8.83 s (1H, N^2H), 11.49 br.s (1H, N^5H). ^{13}C NMR spectrum, δ_C, ppm: 50.6 (CH), 80.7, 91.6, 93.6, 114.9, 126.6 (CH), 128.6 (CH), 129.1, 138.5, 151.8, 162.2, 165.1, 167.6. Mass spectrum, *m*/*z* (I_{rel}, %): 296 (12) $[M]^+$, 265 (48) $[M - OCH_3]^+$, 248 (17), 187 (17), 57 (100). Found, %: C 60.87; H 4.06; N 18.86. $C_{15}H_{12}N_4O_3$. Calculated, %: C 60.81; H 4.08; N 18.91. *M* 296.09.

Compounds **3b**–**3f** were synthesized in a similar way using the corresponding alcohol.

4-Amino-1-ethoxy-3,6-dioxo-1-phenyl-2,3,5,6-tetrahydro-1*H*-pyrrolo[3,4-*c*]pyridine-7-carbonitrile (3b). Yield 0.347 g (56%), white powder, mp 199–201°C (decomp.). IR spectrum, ν, cm^{-1}: 3439, 3381, 3207, 3198 (NH, NH_2), 2220 (C≡N), 1704, 1614 (C=O). ^1H NMR spectrum, δ, ppm: 1.24 t (3H, CH_3, ^3J = 7.1 Hz), 3.23–3.31 m (1H, OCH_2), 3.51–3.59 (1H, OCH_2), 7.30–7.65 m (7H, H_{arom}, NH_2), 8.85 s (1H, N^2H), 11.47 br.s (1H, N^5H). ^{13}C NMR spectrum, δ_C, ppm: 15.6 (CH), 58.8 (CH), 80.6, 91.2, 93.5, 114.9, 126.6 (CH), 128.6 (CH), 129.1, 138.8, 151.9, 162.3, 165.8, 167.6. Mass spectrum, *m*/*z* (I_{rel}, %): 310 (10) $[M]^+$, 265 (100) $[M - OC_2H_5]^+$, 248 (22), 149 (46), 77 (71). Found, %: C 61.88; H 4.57; N 18.03. $C_{16}H_{14}N_4O_3$. Calculated, %: C 61.93; H 4.55; N 18.06. *M* 310.11.

4-Amino-3,6-dioxo-1-phenyl-1-propoxy-2,3,5,6-tetrahydro-1*H*-pyrrolo[3,4-*c*]pyridine-7-carbonitrile (3c). Yield 0.395 g (61%), white powder, mp 196–198°C (decomp.). IR spectrum, ν, cm^{-1}: 3513, 3437, 3306, 3244 (NH, NH_2), 2224 (C≡N), 1710, 1661 (C=O). ^1H NMR spectrum, δ, ppm: 0.98 t (3H, CH_3, ^3J = 7.3 Hz), 1.60–1.67 m (2H, CH_2), 3.13–3.19 m (1H, OCH_2), 3.45–3.51 m (1H, OCH_2), 7.20–7.70 m (7H, H_{arom}, NH_2), 8.85 s (1H, N^2H), 11.48 br.s (1H, N^5H). ^{13}C NMR spectrum, δ_C, ppm: 11.3 (CH), 23.0 (CH), 64.5 (CH), 80.7, 91.0, 93.4, 114.9, 126.6 (CH), 128.6 (CH), 129.1, 138.8, 151.7, 162.3, 165.6, 167.5. Mass spectrum, *m*/*z* (I_{rel}, %): 324 (5) $[M]^+$, 265 (27) $[M - OC_3H_7]^+$, 149 (14), 57 (100). Found, %: C 62.91; H 4.99; N 17.25. $C_{17}H_{16}N_4O_3$. Calculated, %: C 62.95; H 4.97; N 17.27. *M* 324.12.

4-Amino-3,6-dioxo-1-phenyl-1-(propan-2-yloxy)-2,3,5,6-tetrahydro-1*H*-pyrrolo[3,4-*c*]pyridine-7-carbonitril (3d). Yield 0.343 g (53%), white powder, mp 198–200°C (decomp.). IR spectrum, ν, cm^{-1}: 3513, 3406, 3279 (NH, NH_2), 2219 (C≡N), 1687 (C=O). ^1H NMR spectrum, δ, ppm: 1.18 d (3H, CH_3, ^3J = 6.1 Hz), 1.22 d (3H, CH_3, ^3J = 5.8 Hz), 3.67–3.75 m (1H, OCH_2), 7.32–7.65 m (7H, H_{arom}, NH_2), 8.93 s (1H, N^2H), 11.50 br.s (1H, N^5H). ^{13}C NMR spectrum, δ_C, ppm: 23.9 (CH), 25.1 (CH), 62.5 (CH), 62.4 (CH), 67.0 (CH), 80.9, 91.0, 93.6, 115.2, 126.6 (CH), 128.5 (CH), 129.0, 139.3, 151.5, 162.3, 166.3, 167.3. Mass spectrum, *m*/*z* (I_{rel}, %): 324 (8.4) $[M]^+$, 265 (100) $[M - OC_3H_7]^+$, 248 (19.7), 205 (16.4), 105 (24.2), 77 (48.8). Found, %: C 62.93; H 4.98; N 17.24. $C_{17}H_{16}N_4O_3$. Calculated, %: C 62.95; H 4.97; N 17.27. *M* 324.12.

4-Amino-1-butoxy-3,6-dioxo-1-phenyl-2,3,5,6-tetrahydro-1*H*-pyrrolo[3,4-*c*]pyridine-7-carbonitrile (3e). Yield 0.453 g (67%), white powder, mp 197–199°C (decomp.). IR spectrum, ν, cm^{-1}: 3407, 3279, 3244 (NH, NH_2), 2219 (C≡N), 1709, 1675 (C=O). ^1H NMR spectrum, δ, ppm: 0.91 t (3H, CH_3, ^3J = 7.3 Hz), 1.45 non (2H, CH_2, ^3J = 7.3 Hz), 1.56–1.65 m (2H, CH_2), 3.16–3.24 m (1H, OCH_2), 3.48–3.55 m (1H, OCH_2), 7.30–7.60 m (7H, H_{arom}, NH_2), 8.84 s (1H, N^2H), 11.48 br.s (1H, N^5H). ^{13}C NMR spectrum, δ_C, ppm: 14.2 (CH), 19.4 (CH), 31.8 (CH), 62.4 (CH), 80.7, 91.0, 93.4, 114.8, 126.6 (CH), 128.6 (CH), 129.1, 138.8, 151.7, 162.2, 165.7, 167.5. Mass spectrum, *m*/*z* (I_{rel}, %): 338 (7) $[M]^+$, 265 (91) $[M - OC_4H_9]^+$, 248 (26), 105 (23), 57 (100). Found, %: C 63.93; H 5.37; N 16.51. $C_{18}H_{18}N_4O_3$. Calculated, %: C 63.89; H 5.36; N 16.56. *M* 338.14.

4-Amino-1-(2-methylpropyloxy)-3,6-dioxo-1-phenyl-2,3,5,6-tetrahydro-1*H*-pyrrolo[3,4-*c*]pyridine-7-carbonitrile (3f). Yield 0.480 g (71%), white powder, mp 179–181°C (decomp.). IR spectrum, ν, cm^{-1}: 3423, 3266, 3248 (NH, NH_2), 2218 (C≡N), 1710, 1675 (C=O). ^1H NMR spectrum, δ, ppm: 0.95 d (3H, CH_3, ^3J = 6.7 Hz), 0.98 d (3H, CH_3, ^3J = 6.7 Hz), 1.91 sept (1H, CH, ^3J = 6.6 Hz), 2.93–2.99 m (1H, CH_2), 3.30–3.33 m (1H, OCH_2) (the signal was partially overlapped by the water signal), 7.30–7.60 m (7H, H_{arom}, NH_2), 8.83 s (1H, N^2H), 11.50 br.s (1H, N^5H). ^{13}C NMR spectrum, δ_C, ppm: 19.8 (CH), 20.0 (CH), 28.6 (CH), 69.1 (CH), 80.7 (CH), 90.9, 93.4, 114.9, 126.6 (CH), 128.6 (CH), 129.1, 138.9, 151.8, 162.3, 165.5, 167.5. Mass spectrum, *m*/*z* (I_{rel}, %): 338 (7) $[M]^+$, 265 (48) $[M - OC_4H_9]^+$, 248 (12), 105 (16), 57 (100). Found, %: C 63.90; H 5.37; N 16.52. $C_{18}H_{18}N_4O_3$. Calculated, %: C 63.89; H 5.36; N 16.56. *M* 338.14.

The purity of the isolated compounds was checked by TLC on Sorbfil PTSH-AF-A-UF plates; spots were visualized under UV light (λ 254, 365 nm) and by

thermal decomposition. The IR spectra were recorded in mineral oil on an FSM-1202 spectrometer with Fourier transform. The ^{1}H and ^{13}C NMR spectra were measured on a Bruker Avance III HD 400 spectrometer at 400 MHz and 101 MHz, respectively, using DMSO-d_6 as solvent and tetramethylsilane as internal standard. The mass spectra (electron impact, 70 eV) were obtained with a Shimadzu GCMS-QP 2010 SE instrument. Elemental analyses were carried out on a Vario MICRO cube CHN analyzer. The melting points were determined using an Electrothermal IA 9000 series II melting point apparatus. 4-Amino-1-hydroxy-3,6-dioxo-1-phenyl-2,3,5,6-tetrahydro-1*H*-pirrolo[3,4-*c*]pyridine-7-carbonitrile (**2**) was synthesized according to [4].

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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