

# New Efficient Synthesis of 6-Aminopyrano[3,4-*c*]pyridines via Smiles Type Rearrangement

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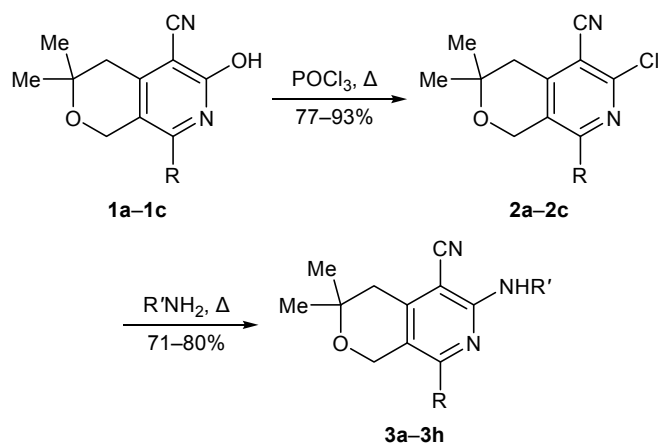
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**Abstract**—A new efficient procedure has been developed for the synthesis of 6-aminopyrano[3,4-*c*]pyridines via Smiles type rearrangement. The procedure is characterized by improved overall yield and avoidance of experimentally difficult chlorination step.

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Taking into account the results of biological testing of 6-aminopyrano[3,4-*c*]pyridines [1–3] and published data [4, 5], we have developed a new, more efficient procedure for the synthesis of these compounds. 6-Aminopyrano[3,4-*c*]pyridines were previously obtained by a classical method based on nucleophilic substitution of the chlorine atom in 6-chloropyrano[3,4-*c*]pyridines **2a–2c** [1, 2, 6] by various amines. Compounds **2a–2c** were prepared in turn by reaction of the corresponding 8-alkyl(aryl)-6-hydroxy-3,3-dimethyl-3,4-dihydro-1*H*-pyrano[3,4-*c*]pyridine-5-carbonitriles **1a–1c** [7] with phosphoryl chloride.

**Scheme 1.**

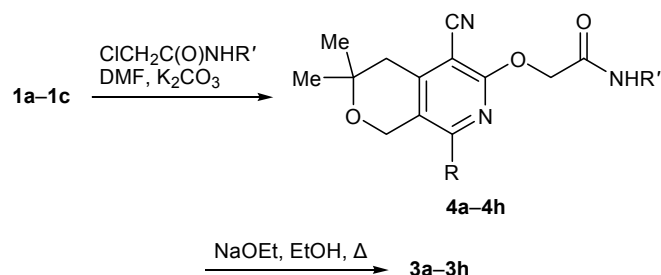


**1, 2**, R = Me (**a**), Bu (**b**), Ph (**c**); **3**, R = Me, R' = H (**a**), PhCH<sub>2</sub> (**b**), furan-2-ylmethyl (**c**); R = Bu, R' = H (**d**), furan-2-ylmethyl (**e**), tetrahydrofuran-2-ylmethyl (**f**), PhCH<sub>2</sub>CH<sub>2</sub> (**g**); R = Ph, R' = H (**h**).

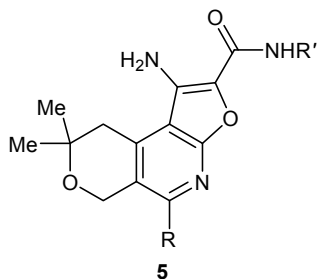
Nucleophilic substitution of the chlorine atom in compounds **2** requires harsh conditions, in particular heating under reflux in excess amine or (with ammonia) at 180°C under pressure. The target 8-alkyl(aryl)-6-amino-3,3-dimethyl-3,4-dihydro-1*H*-pyrano[3,4-*c*]pyridine-5-carbonitriles **3a–3h** are thus obtained in ~65% yield over two steps (Scheme 1).

Herein we propose a new efficient method for the synthesis of pyrano[3,4-*c*]pyridines **3a–3h** which attract interest as potential biologically active compounds. The procedure is based on the Smiles type rearrangement recently discovered by us [8, 9]. The initial compounds were 2-[(8-alkyl(aryl)-5-cyano-3,3-dimethyl-3,4-dihydro-1*H*-pyrano[3,4-*c*]pyridin-6-yl)-oxy]acetamides **4a–4h** which were obtained by alkylation of 6-hydroxy derivatives **1a–1c** with the corresponding chloroacetamides. Rearrangement of acetamides **4a–4h** on heating in ethanol in the presence of sodium ethoxide afforded target nitriles **3a–3h** in an overall yield of ~70% (Scheme 2).

**Scheme 2.**



However, the proposed procedure is applicable to the synthesis of compounds **3** only from chloroacetamides with an aliphatic substituent on the nitrogen atom, whereas in other cases (*N,N*-disubstituted chloroacetamides or *N*-aryl derivatives) the reaction was accompanied by intramolecular cyclization with formation of fused furans **5** [8, 9].



The structure of amino derivatives **3a–3h** was confirmed by IR spectra which clearly showed a CN stretching vibration band at 2208–2218  $\text{cm}^{-1}$ ; the presence of a cyano group indicated that no cyclization to structure **5** occurred [8, 9]. The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra and elemental analyses of **3a–3h** were also consistent with their structure.

The proposed procedure is advantageous due to experimental simplicity (laborious chlorination of 6-hydroxypyranopyridines is avoided) and fairly mild conditions (there is no need of high pressure in the synthesis of ammonia and low-boiling amine derivatives).

## EXPERIMENTAL

The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on a Varian Mercury 300VX spectrometer at 300 and 75 MHz, respectively, using tetramethylsilane as internal standard. The IR spectra were measured on a Nicolet Avatar 330-FT-IR spectrometer from samples dispersed in mineral oil. The elemental analyses were obtained by the Korshun–Klimova (C, H) and Dumas–Pregl methods (N). The melting points were determined with a Boetius micro hot stage.

**Compounds 4a–4h (general procedure).** The corresponding chloroacetamide, 12 mmol, was added with stirring to a suspension of 10 mmol of compound **1a–1c** and 1.66 g (12 mmol) of  $\text{K}_2\text{CO}_3$  in 25 mL of anhydrous DMF. The mixture was stirred for 2 h at 100°C, cooled to room temperature, and poured into cold water. The precipitate was filtered off, washed with water, dried, and recrystallized from ethanol.

**2-[(5-Cyano-3,3,8-trimethyl-3,4-dihydro-1H-pyrano[3,4-c]pyridin-6-yl)oxy]acetamide (4a).** Yield

79%, mp 122–124°C. IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 3443, 3216 ( $\text{NH}_2$ ), 2235 ( $\text{C}\equiv\text{N}$ ), 1692 ( $\text{C}=\text{O}$ ).  $^1\text{H}$  NMR spectrum ( $\text{CDCl}_3$ ),  $\delta$ , ppm: 1.32 s (6H, 3-Me), 2.37 s (3H, 8-Me), 2.83 s (2H,  $\text{CH}_2$ ), 4.64 s (2H,  $\text{OCH}_2$ ), 4.89 s (2H,  $\text{CH}_2\text{CO}$ ), 5.63 br and 6.44 br (1H each,  $\text{NH}_2$ ).  $^{13}\text{C}$  NMR spectrum ( $\text{DMSO}-d_6$ – $\text{CCl}_4$ , 1:3),  $\delta_c$ , ppm: 20.8 ( $\text{CH}_3$ ), 25.9 (2C,  $\text{CH}_3$ ), 37.7 ( $\text{CH}_2$ ), 45.2 ( $\text{OCH}_2\text{CO}$ ), 59.3 ( $\text{C}^1$ ), 64.1 ( $\text{CO}$ ), 68.9 ( $\text{C}^3$ ), 87.0 ( $\text{C}^5$ ), 115.5 (CN), 115.6, 144.9, 157.1, 158.0. Found, %: C 60.76; H 6.41; N 15.03.  $\text{C}_{14}\text{H}_{17}\text{N}_3\text{O}_3$ . Calculated, %: C 61.08; H 6.22; N 15.26.

**N-Benzyl-2-[(5-cyano-3,3,8-trimethyl-3,4-dihydro-1H-pyrano[3,4-c]pyridin-6-yl)oxy]acetamide (4b).** Yield 80%, mp 161–162°C. IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 3278, 3102 (NH), 2222 ( $\text{C}\equiv\text{N}$ ), 1667 ( $\text{C}=\text{O}$ ).  $^1\text{H}$  NMR spectrum ( $\text{CDCl}_3$ ),  $\delta$ , ppm: 1.32 s (6H, 3- $\text{CH}_3$ ), 2.37 s (3H, 8- $\text{CH}_3$ ), 2.83 s (2H,  $\text{CH}_2$ ), 4.51 s (2H,  $\text{OCH}_2$ ), 4.55 s (2H,  $\text{CH}_2\text{CO}$ ), 4.83 br (2H,  $\text{NHCH}_2$ ), 7.14–7.31 m (5H, Ph), 8.36 br (1H, NH). Found, %: C 68.75; H 6.49; N 11.69.  $\text{C}_{21}\text{H}_{23}\text{N}_3\text{O}_3$ . Calculated, %: C 69.02; H 6.34; N 11.50.

**2-[(5-Cyano-3,3,8-trimethyl-3,4-dihydro-1H-pyrano[3,4-c]pyridin-6-yl)oxy]-N-(furan-2-ylmethyl)acetamide (4c).** Yield 86%, mp 141–143°C. IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 3301, 3078 (NH), 2220 ( $\text{C}\equiv\text{N}$ ), 1661 ( $\text{C}=\text{O}$ ).  $^1\text{H}$  NMR spectrum ( $\text{DMSO}-d_6$ – $\text{CCl}_4$ , 1:3),  $\delta$ , ppm: 1.29 s (6H, 3-Me), 2.23 s (3H, 8- $\text{CH}_3$ ), 2.71 s (2H,  $\text{CH}_2$ ), 4.33 d (2H,  $\text{NHCH}_2$ ,  $J = 5.6$  Hz), 4.54 s (2H,  $\text{OCH}_2$ ), 4.80 s (2H,  $\text{CH}_2\text{CO}$ ), 6.24 d.d (1H, 3'-H,  $J = 3.3$ , 0.8 Hz), 6.32 d.d (1H, 4'-H,  $J = 3.3$ , 1.8 Hz), 7.42 d.d (1H, 5'-H,  $J = 1.8$ , 0.8 Hz), 8.62 t (1H, NH,  $J = 5.6$  Hz). Found, %: C 64.46; H 6.11; N 11.62.  $\text{C}_{19}\text{H}_{21}\text{N}_3\text{O}_4$ . Calculated, %: C 64.21; H 5.96; N 11.82.

**2-[(8-Butyl-5-cyano-3,3-dimethyl-3,4-dihydro-1H-pyrano[3,4-c]pyridin-6-yl)oxy]acetamide (4d).** Yield 83%, mp 179–180°C. IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 3420, 3182 ( $\text{NH}_2$ ), 2239 ( $\text{C}\equiv\text{N}$ ), 1698 ( $\text{C}=\text{O}$ ).  $^1\text{H}$  NMR spectrum ( $\text{DMSO}-d_6$ – $\text{CCl}_4$ , 1:3),  $\delta$ , ppm: 0.95 t (3H,  $\text{CH}_3$ ,  $J = 7.3$  Hz), 1.27 s (6H, 3-Me), 1.31–1.44 m (2H,  $\text{CH}_2\text{CH}_3$ ), 1.63–1.73 m (2H,  $\text{CH}_2\text{C}_2\text{H}_5$ ), 2.55 t (2H, 8- $\text{CH}_2$ ,  $J = 7.5$  Hz), 2.77 s (2H,  $\text{CH}_2$ ), 4.62 s (2H,  $\text{OCH}_2$ ), 4.76 s (2H,  $\text{CH}_2\text{CO}$ ), 6.98 br and 7.07 br (1H each,  $\text{NH}_2$ ). Found, %: C 64.02; H 7.50; N 13.48.  $\text{C}_{17}\text{H}_{23}\text{N}_3\text{O}_3$ . Calculated, %: C 64.33; H 7.30; N 13.24.

**2-[(8-Butyl-5-cyano-3,3-dimethyl-3,4-dihydro-1H-pyrano[3,4-c]pyridin-6-yl)oxy]-N-(furan-2-ylmethyl)acetamide (4e).** Yield 87%, mp 113–115°C. IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 3266, 3083 (NH), 2224 ( $\text{C}\equiv\text{N}$ ), 1655 ( $\text{C}=\text{O}$ ).  $^1\text{H}$  NMR spectrum ( $\text{DMSO}-d_6$ – $\text{CCl}_4$ , 1:3),  $\delta$ , ppm: 0.94 t (3H,  $\text{CH}_3$ ,  $J = 7.3$  Hz), 1.28 s (6H,

3-Me), 1.31–1.42 m (2H, CH<sub>2</sub>CH<sub>3</sub>), 1.58–1.69 m (2H, CH<sub>2</sub>C<sub>2</sub>H<sub>5</sub>), 2.52 t (2H, 8-CH<sub>2</sub>, *J* = 7.4 Hz), 2.77 s (2H, CH<sub>2</sub>), 4.31 t (2H, NHCH<sub>2</sub>, *J* = 5.7 Hz), 4.62 s (2H, OCH<sub>2</sub>), 4.82 s (2H, CH<sub>2</sub>CO), 6.16 d.d (1H, 3'-H, *J* = 3.2, 0.9 Hz), 6.29 d.d (1H, 4'-H, *J* = 3.2, 1.8 Hz), 7.37 d.d (1H, 5'-H, *J* = 1.8, 0.9 Hz), 8.16 t (1H, NH, *J* = 5.7 Hz). Found, %: C 66.25; H 6.69; N 10.75. C<sub>22</sub>H<sub>27</sub>N<sub>3</sub>O<sub>4</sub>. Calculated, %: C 66.48; H 6.85; N 10.57.

**2-[(8-Butyl-5-cyano-3,3-dimethyl-3,4-dihydro-1H-pyrano[3,4-c]pyridin-6-yl)oxy]-N-(tetrahydrofuran-2-ylmethyl)acetamide (4f).** Yield 89%, mp 80–82°C. IR spectrum,  $\nu$ , cm<sup>-1</sup>: 3275, 3089 (NH), 2225 (C≡N), 1660 (C=O). <sup>1</sup>H NMR spectrum (DMSO-*d*<sub>6</sub>-CCl<sub>4</sub>, 1:3),  $\delta$ , ppm: 0.94 t (3H, CH<sub>3</sub>, *J* = 7.3 Hz), 1.27 s (6H, 3-Me), 1.30–1.42 m (2H, CH<sub>2</sub>CH<sub>3</sub>), 1.45–1.59 m (1H) and 1.79–1.95 m (3H) (3'-H, 4'-H), 1.60–1.71 m (2H, CH<sub>2</sub>C<sub>2</sub>H<sub>5</sub>), 2.53 t (2H, 8-CH<sub>2</sub>, *J* = 7.4 Hz), 2.77 s (2H, CH<sub>2</sub>), 3.16 d.t (1H, NHCH<sub>2</sub>, *J* = 13.5, 6.0 Hz), 3.27 d.d.d (1H, NHCH<sub>2</sub>, *J* = 13.5, 5.8, 4.8 Hz), 3.60–3.68 m and 3.76–3.82 m (1H each, 5'-H), 3.82–3.91 m (1H, 2'-H), 4.62 s (2H, OCH<sub>2</sub>), 4.78 s (2H, CH<sub>2</sub>CO), 7.59 t (1H, NH, *J* = 5.8 Hz). Found, %: C 66.09; H 7.92; N 10.68. C<sub>22</sub>H<sub>31</sub>N<sub>3</sub>O<sub>4</sub>. Calculated, %: C 65.81; H 7.78; N 10.47.

**2-[(8-Butyl-5-cyano-3,3-dimethyl-3,4-dihydro-1H-pyrano[3,4-c]pyridin-6-yl)oxy]-N-(2-phenylethyl)acetamide (4g).** Yield 90%, mp 120–121°C. IR spectrum,  $\nu$ , cm<sup>-1</sup>: 3427, 3276, 3099 (NH), 2221 (C≡N), 1665 (C=O). <sup>1</sup>H NMR spectrum (DMSO-*d*<sub>6</sub>-CCl<sub>4</sub>, 1:3),  $\delta$ , ppm: 0.94 t (3H, CH<sub>3</sub>, *J* = 7.3 Hz), 1.28 s (6H, 3-Me), 1.31–1.42 m (2H, CH<sub>2</sub>CH<sub>3</sub>), 1.60–1.71 m (2H, CH<sub>2</sub>C<sub>2</sub>H<sub>5</sub>), 2.53 t (2H, 8-CH<sub>2</sub>, *J* = 7.5 Hz), 2.72–2.77 m (2H, CH<sub>2</sub>Ph), 2.78 s (2H, CH<sub>2</sub>), 3.31–3.39 m (2H, NHCH<sub>2</sub>), 4.62 s (2H, OCH<sub>2</sub>), 4.76 s (2H, CH<sub>2</sub>CO), 7.10–7.25 m (5H, Ph), 7.63 t (1H, NH, *J* = 5.7 Hz). Found, %: C 70.97; H 7.59; N 9.75. C<sub>25</sub>H<sub>31</sub>N<sub>3</sub>O<sub>3</sub>. Calculated, %: C 71.23; H 7.41; N 9.97.

**2-[(5-Cyano-3,3-dimethyl-8-phenyl-3,4-dihydro-1H-pyrano[3,4-c]pyridin-6-yl)oxy]acetamide (4h).** Yield 81%, mp 99–101°C. IR spectrum,  $\nu$ , cm<sup>-1</sup>: 3442, 3164 (NH<sub>2</sub>), 2232 (C≡N), 1694 (C=O). <sup>1</sup>H NMR spectrum (CDCl<sub>3</sub>),  $\delta$ , ppm: 1.37 s (6H, 3-Me), 2.94 s (2H, CH<sub>2</sub>), 4.73 s (2H, OCH<sub>2</sub>), 4.96 s (2H, CH<sub>2</sub>CO), 5.66 br and 6.47 br (1H each, NH<sub>2</sub>), 7.40–7.51 m (5H, Ph). Found, %: C 67.96; H 5.47; N 12.71. C<sub>19</sub>H<sub>19</sub>N<sub>3</sub>O<sub>3</sub>. Calculated, %: C 67.64; H 5.68; N 12.46.

**Compounds 3a–3h (general procedures).** *a.* Compound **4a–4h**, 10 mmol, was added to a solution of sodium ethoxide prepared from 0.12 g (5 mmol) of sodium and 30 mL of anhydrous ethanol. The mixture

was refluxed for 1 h, cooled, and poured onto ice, and the precipitate was filtered off, washed with water, dried, and recrystallized from ethanol.

*b.* Compounds **3b**, **3c**, and **3e–3g**. A mixture of 10 mmol of compound **2a–2c** and 100 mmol of the corresponding amine was refluxed for 4 h. The mixture was cooled and diluted with 100 mL of water, and the precipitate was treated as described above in *a*.

*c.* Compounds **3a**, **3d**, and **3h**. A mixture of 10 mmol of compound **2a–2c** and 50 mL of 20% ethanolic ammonia was heated for 18 h at 180°C in a steel bomb. The mixture was cooled, the solvent was distilled off, the residue was treated with water, and the precipitate was treated as described above in *a*.

**6-Amino-3,3,8-trimethyl-3,4-dihydro-1H-pyrano[3,4-c]pyridine-5-carbonitrile (3a).** Yield 79 (*a*), 71% (*c*); mp 220–221°C. IR spectrum,  $\nu$ , cm<sup>-1</sup>: 3471, 3289 (NH<sub>2</sub>), 2214 (C≡N). <sup>1</sup>H NMR spectrum (DMSO-*d*<sub>6</sub>-CCl<sub>4</sub>, 1:3),  $\delta$ , ppm: 1.25 s (6H, 3-Me), 2.20 s (3H, 8-CH<sub>3</sub>), 2.62 s (2H, CH<sub>2</sub>), 4.49 s (2H, OCH<sub>2</sub>), 6.06 br.s (2H, NH<sub>2</sub>). <sup>13</sup>C NMR spectrum (DMSO-*d*<sub>6</sub>-CCl<sub>4</sub>, 1:3),  $\delta_c$ , ppm: 20.6 (CH<sub>3</sub>), 25.8 (2C, CH<sub>3</sub>), 37.5 (CH<sub>2</sub>), 59.3 (OCH<sub>2</sub>), 68.9 (C<sup>3</sup>), 87.0 (CCN), 115.3 (CN), 115.9, 145.9, 156.3, 158.2. Found, %: C 66.05; H 6.79; N 19.55. C<sub>12</sub>H<sub>15</sub>N<sub>3</sub>O. Calculated, %: C 66.34; H 6.96; N 19.34.

**6-(Benzylamino)-3,3,8-trimethyl-3,4-dihydro-1H-pyrano[3,4-c]pyridine-5-carbonitrile (3b).** Yield 84 (*a*), 75% (*b*); mp 178–179°C. IR spectrum,  $\nu$ , cm<sup>-1</sup>: 3390 (NH), 2218 (C≡N). <sup>1</sup>H NMR spectrum (DMSO-*d*<sub>6</sub>-CCl<sub>4</sub>, 1:3),  $\delta$ , ppm: 1.21 s (6H, 3-CH<sub>3</sub>), 2.22 s (3H, 8-CH<sub>3</sub>), 2.64 s (2H, CH<sub>2</sub>), 4.51 s (2H, OCH<sub>2</sub>), 4.71 d (2H, NHCH<sub>2</sub>, *J* = 6.1 Hz), 7.25–7.35 m (5H, Ph), 7.50 t (1H, NH, *J* = 6.1 Hz). <sup>13</sup>C NMR spectrum (DMSO-*d*<sub>6</sub>-CCl<sub>4</sub>, 1:3),  $\delta_c$ , ppm: 20.3 (CH<sub>3</sub>), 25.7 (2C, CH<sub>3</sub>), 37.9 (CH<sub>2</sub>), 59.8 (OCH<sub>2</sub>), 61.4 (CH<sub>2</sub>Ph), 68.4 (C<sup>3</sup>), 87.6 (CCN), 115.0 (CN), 115.7, 126.5, 128.2, 128.7, 137.9, 145.7, 156.8, 158.5. Found, %: C 74.49; H 6.74; N 13.49. C<sub>19</sub>H<sub>21</sub>N<sub>3</sub>O. Calculated, %: C 74.24; H 6.89; N 13.67.

**6-[(Furan-2-ylmethyl)amino]-3,3,8-trimethyl-3,4-dihydro-1H-pyrano[3,4-c]pyridine-5-carbonitrile (3c).** Yield 81 (*a*), 78% (*b*); mp 169–171°C. IR spectrum,  $\nu$ , cm<sup>-1</sup>: 3363 (NH), 2212 (C≡N). <sup>1</sup>H NMR spectrum (DMSO-*d*<sub>6</sub>-CCl<sub>4</sub>, 1:3),  $\delta$ , ppm: 1.25 s (6H, 3-CH<sub>3</sub>), 2.25 s (3H, 8-CH<sub>3</sub>), 2.63 s (2H, CH<sub>2</sub>), 4.50 s (2H, OCH<sub>2</sub>), 4.60 d (2H, NHCH<sub>2</sub>, *J* = 5.8 Hz), 6.17 d.d (1H, 3'-H, *J* = 3.3, 0.8 Hz), 6.26 d.d (1H, 4'-H, *J* = 3.3, 1.8 Hz), 6.77 t (1H, NH, *J* = 5.8 Hz), 7.34 d.d (1H,

5'-H,  $J = 1.8, 0.8$  Hz). Found, %: C 68.94; H 6.57; N 13.91.  $C_{17}H_{19}N_3O_2$ . Calculated, %: C 68.67; H 6.44; N 14.13.

**6-Amino-8-butyl-3,3-dimethyl-3,4-dihydro-1H-pyrano[3,4-c]pyridine-5-carbonitrile (3d).** Yield 79 (a), 76% (c); mp 165–167°C. IR spectrum,  $\nu$ ,  $cm^{-1}$ : 3475, 3262 (NH<sub>2</sub>), 2210 (C≡N). <sup>1</sup>H NMR spectrum (DMSO- $d_6$ -CCl<sub>4</sub>, 1:3),  $\delta$ , ppm: 0.94 t (3H, CH<sub>3</sub>,  $J = 7.3$  Hz), 1.25 s (6H, 3-Me), 1.31–1.44 m (2H, CH<sub>2</sub>CH<sub>3</sub>), 1.54–1.65 m (2H, CH<sub>2</sub>C<sub>2</sub>H<sub>5</sub>), 2.39–2.45 m (2H, 8-CH<sub>2</sub>), 2.62 s (2H, CH<sub>2</sub>), 4.53 s (2H, OCH<sub>2</sub>), 6.02 br (2H, NH<sub>2</sub>). Found, %: C 69.16; H 7.97; N 16.44.  $C_{15}H_{21}N_3O$ . Calculated, %: C 69.47; H 8.16; N 16.20.

**8-Butyl-6-[(furan-2-ylmethyl)amino]-3,3-dimethyl-3,4-dihydro-1H-pyrano[3,4-c]pyridine-5-carbonitrile (3e).** Yield 82 (a), 73% (b); mp 135–136°C. IR spectrum,  $\nu$ ,  $cm^{-1}$ : 3363 (NH), 2216 (C≡N). <sup>1</sup>H NMR spectrum (DMSO- $d_6$ -CCl<sub>4</sub>, 1:3),  $\delta$ , ppm: 0.93 t (3H, CH<sub>3</sub>,  $J = 7.3$  Hz), 1.25 s (6H, 3-CH<sub>3</sub>), 1.31–1.42 m (2H, CH<sub>2</sub>CH<sub>3</sub>), 1.58–1.69 m (2H, CH<sub>2</sub>C<sub>2</sub>H<sub>5</sub>), 2.45 t (2H, 8-CH<sub>2</sub>,  $J = 7.5$  Hz), 2.63 s (2H, CH<sub>2</sub>), 4.53 s (2H, OCH<sub>2</sub>), 4.59 d (2H, NHCH<sub>2</sub>,  $J = 5.7$  Hz), 6.14 d.d (1H, 3'-H,  $J = 3.1, 0.8$  Hz), 6.25 d.d (1H, 4'-H,  $J = 3.1, 1.8$  Hz), 6.84 t (1H, NHCH<sub>2</sub>,  $J = 5.7$  Hz), 7.33 d.d (1H, 5'-H,  $J = 1.8, 0.8$  Hz). Found, %: C 70.54; H 7.31; N 12.22.  $C_{20}H_{25}N_3O_2$ . Calculated, %: C 70.77; H 7.42; N 12.38.

**8-Butyl-3,3-dimethyl-6-[(tetrahydrofuran-2-ylmethyl)amino]-3,4-dihydro-1H-pyrano[3,4-c]pyridine-5-carbonitrile (3f).** Yield 85 (a), 80% (b); mp 98–100°C. IR spectrum,  $\nu$ ,  $cm^{-1}$ : 3357 (NH), 2211 (C≡N). <sup>1</sup>H NMR spectrum (CDCl<sub>3</sub>),  $\delta$ , ppm: 0.95 t (3H, CH<sub>3</sub>,  $J = 7.3$  Hz), 1.29 s (6H, 3-CH<sub>3</sub>), 1.32–1.45 m (2H, CH<sub>2</sub>CH<sub>3</sub>), 1.58–1.65 m (1H) and 1.87–2.06 m (3H) (3'-H, 4'-H), 1.61–1.72 m (2H, CH<sub>2</sub>C<sub>2</sub>H<sub>5</sub>), 2.45–2.51 m (2H, 8-CH<sub>2</sub>), 2.71 s (2H, CH<sub>2</sub>), 3.54 d.d.d (1H, NHCH<sub>2</sub>,  $J = 13.6, 6.6, 5.4$  Hz), 3.74 d.d.d (1H, NHCH<sub>2</sub>,  $J = 13.6, 6.0, 4.0$  Hz), 3.76–3.82 m and 3.88–3.96 m (1H each, 5'-H), 4.07–4.15 m (1H, 2'-H), 4.63 s (2H, OCH<sub>2</sub>), 5.30 br (1H, NH). Found, %: C 70.22; H 8.35; N 12.44.  $C_{20}H_{29}N_3O_2$ . Calculated, %: C 69.94; H 8.51; N 12.23.

**8-Butyl-3,3-dimethyl-6-[(2-phenylethyl)amino]-3,4-dihydro-1H-pyrano[3,4-c]pyridine-5-carbonitrile (3g).** Yield 80 (a), 77% (b); mp 121–123°C. IR

spectrum,  $\nu$ ,  $cm^{-1}$ : 3359 (NH), 2213 (C≡N). <sup>1</sup>H NMR spectrum (DMSO- $d_6$ -CCl<sub>4</sub>, 1:3),  $\delta$ , ppm: 0.97 t (3H, CH<sub>3</sub>,  $J = 7.3$  Hz), 1.26 s (6H, 3-CH<sub>3</sub>), 1.35–1.48 m (2H, CH<sub>2</sub>CH<sub>3</sub>), 1.66–1.77 m (2H, CH<sub>2</sub>C<sub>2</sub>H<sub>5</sub>), 2.49 t (2H, 8-CH<sub>2</sub>,  $J = 7.4$  Hz), 2.62 s (2H, CH<sub>2</sub>), 2.83–2.92 m (2H, CH<sub>2</sub>Ph), 3.57–3.65 m (2H, NHCH<sub>2</sub>), 4.54 s (2H, OCH<sub>2</sub>), 6.45 t (1H, NH,  $J = 5.8$  Hz), 7.10–7.27 m (5H, Ph). Found, %: C 75.67; H 8.22; N 11.31.  $C_{23}H_{29}N_3O$ . Calculated, %: C 76.00; H 8.04; N 11.56.

**6-Amino-3,3-dimethyl-8-phenyl-3,4-dihydro-1H-pyrano[3,4-c]pyridine-5-carbonitrile (3h).** Yield 78 (a), 72% (c); mp 194–195°C. IR spectrum,  $\nu$ ,  $cm^{-1}$ : 3480, 3284 (NH<sub>2</sub>), 2208 (C≡N). <sup>1</sup>H NMR spectrum (DMSO- $d_6$ -CCl<sub>4</sub>, 1:3),  $\delta$ , ppm: 1.30 s (6H, 3-CH<sub>3</sub>), 2.73 s (2H, CH<sub>2</sub>), 4.47 s (2H, OCH<sub>2</sub>), 6.31 br (2H, NH<sub>2</sub>), 7.37–7.45 m (5H, Ph). <sup>13</sup>C NMR spectrum (DMSO- $d_6$ -CCl<sub>4</sub>, 1:3),  $\delta_c$ , ppm: 26.2 (2C, CH<sub>3</sub>), 38.0 (CH<sub>2</sub>), 59.7 (OCH<sub>2</sub>), 69.1 (C<sup>3</sup>), 88.5 (C<sup>5</sup>), 115.2 (CN), 115.9, 127.5, 127.8, 128.1, 138.3, 147.9, 157.4, 158.3. Found, %: C 73.36; H 6.27; N 14.85.  $C_{17}H_{17}N_3O$ . Calculated, %: C 73.10; H 6.13; N 15.04.

## REFERENCES

1. Sirakanyan, S.N., *Doctoral (Chem.) Dissertation*, Yerevan, 2015.
2. Paronikyan, E.G., Sirakanyan, S.N., Noravyan, A.S., and Paronikyan, E.G., *Arm. Khim. Zh.*, 1989, vol. 42, no. 12, p. 766.
3. Paronikyan, E.G., Sirakanyan, S.N., Noravyan, A.S., and Melkonyan, Dzh.A., *Arm. Khim. Zh.*, 1991, vol. 44, no. 4, p. 250.
4. Potnick, J., Int. Patent Appl. no. WO 2014/117919.
5. Foloppe, N., Benwell, K., Brooks, T.D., Kennett, G., and Knight, A.R., *Bioorg. Med. Chem. Lett.*, 2009, vol. 19, p. 4183.
6. Paronikyan, E.G., Sirakanyan, S.N., and Noravyan, A.S., *Chem. Heterocycl. Compd.*, 2003, vol. 39, p. 374.
7. Paronikyan, E.G., Sirakanyan, S.N., Lindeman, S.V., Aleksanyan, M.S., Karapetyan, A.A., Noravyan, A.S., and Struchkov, Yu.T., *Chem. Heterocycl. Compd.*, 1989, vol. 25, p. 953.
8. Sirakanyan, S.N., *Khim. Zh. Arm.*, 2013, vol. 66, no. 2, p. 262.
9. Sirakanyan, S.N., Spinelli, D., Geronikaki, A., Hovakimyan, A.A., and Noravyan, A.S., *Tetrahedron*, 2015, vol. 71, p. 3263.