Synthesis of 5-aminothiazolo[4,5-*b*]pyridine-2-carboxamides

I. V. Zavarzin, N. G. Smirnova, V. N. Yarovenko, and M. M. Krayushkin*

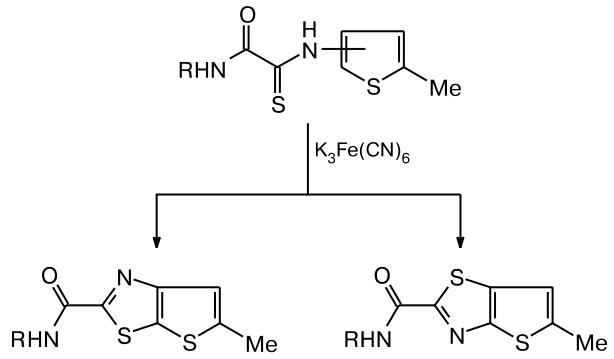
N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences,
47 Leninskii prosp., 119991 Moscow, Russian Federation.
Fax: +7 (095) 135 5328. E-mail: zavi@mail.ioc.ac.ru

A method for the synthesis of 5-aminothiazolo[4,5-*b*]pyridine-2-carboxamides was proposed. The method involves oxidation of monothiooxamides derived from 2,6-diaminopyridine.

Key words: monothiooxamides, aminopyridines, $K_3Fe(CN)_6$, 5-aminothiazolo[4,5-*b*]pyridine-2-carboxamides, *N*-pyridylthiooxamic acids.

Earlier, we have demonstrated that oxidation of compounds in which monothiooxamide fragments are bound to the phenyl or heterocyclic rings affords fused compounds containing a carboxamide function in good yields. It is in this way that carbamoylbenzothiazoles were synthesized.[1] In addition, carbamoylthieno[3,2-*d*]- and [2,3-*d*]thiazoles were obtained from isomeric 2-methylaminothiophenes (Scheme 1).[2,3]

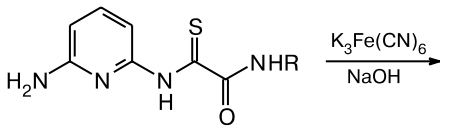
Scheme 1



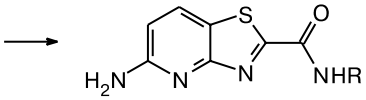
In the present work, this approach was extended to aminopyridines, and previously unknown 5-aminothiazolo[4,5-*b*]pyridine-2-carboxamides were obtained. Thiazolopyridines are reported to exhibit a broad spectrum of biological activity.[4,5] We found a route to this type of derivatives containing a carbamoyl group.

The starting monothiooxamides **1a—d** were prepared according to a known procedure[6] from 2,6-diaminopyridine, the corresponding chloroacetamides, and sulfur in the presence of triethylamine.

Monothiooxamides **1a—d** are oxidized with $K_3Fe(CN)_6$ in 20% NaOH at 50 °C to give 5-aminothiazolo[4,5-*b*]pyridine-2-carboxamides **2a—d** in high yields.



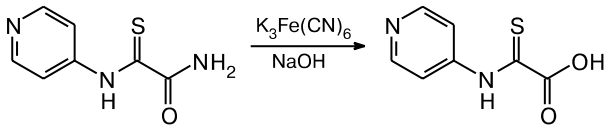
1a—d



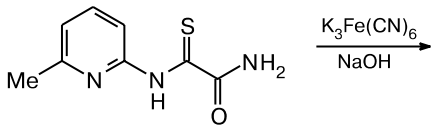
2a—d

R = Ph (**a**), 4-BrC_6H_4 (**b**), 4-ClC_6H_4 (**c**), 4-FC_6H_4 (**d**)

The reaction is sensitive to electronic factors: substituents in the pyridine ring affect the cyclization process. For instance, monothiooxamides **3** and **5** form no thiazole ring, giving *N*-pyridylthiooxamic acids **4** and **6** as the major reaction products.



3 **4**



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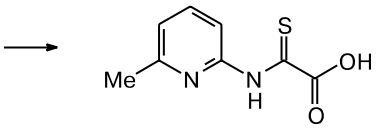

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The structures of compounds **2a—d**, **4**, and **6** were confirmed by elemental analysis, MS, and ^1H NMR data.

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The mass spectra of compounds **2a—d**, **4**, and **6** show molecular ion peaks. The ^{1}H NMR spectra contain, in addition to the signals for the amino and methyl groups and the benzene ring, the signals for the protons of the pyridine rings (δ 6.50—8.22).

Experimental

^{1}H NMR spectra were recorded on a Bruker AC-300 instrument (300 MHz) in $CDCl_3$ and DMSO-d_6. Mass spectra were recorded on a Kratos instrument (direct inlet of the sample, ionizing energy 70 eV, controlling voltage 1.75 kV). Commercial (Acros) chemicals were used. Monothiooxamides **1a—d**, **3**, and **5** were prepared according to a known procedure.[6]

5-Aminothiazolo[4,5-*b*]pyridine-2-carboxamides (2a—d) (general procedure). A corresponding monothiooxamide **1a—d** (0.20 mmol) was dissolved in 20% NaOH (1.68 mmol) and the solution was added dropwise at 50 °C to a stirred solution of $K_3Fe(CN)_6$ (0.14 g, 0.44 mmol) in 4.4 mL of water. The reaction mixture was stirred for an additional 2 h and cooled to ~20 °C. The precipitates of thiazolopyridines **2a—d** that formed were filtered off, washed with water, dried, and recrystallized from 95% EtOH.

5-Aminothiazolo[4,5-*b*]pyridine-2-carboxanilide (2a). Yield 91%, m.p. >300 °C. MS, *m/z*: 270 $[M]^+$. ^{1}H NMR, δ: 6.42 (s, 2 H, NH_2); 6.75 (d, 1 H, pyridine, J = 8.8 Hz); 7.15 (m, 1 H, arom.); 7.40 (m, 2 H, arom.); 7.80 (d, 2 H, arom., J = 8.2 Hz); 8.20 (d, 1 H, pyridine, J = 8.8 Hz); 10.88 (s, 1 H, NH). Found (%): C, 57.50; H, 3.85; N, 20.60; S, 11.98. $C_{13}H_{10}N_4OS$. Calculated (%): C, 57.78; H, 3.70; N, 20.74; S, 11.85.

***N*-(4-Bromophenyl)-5-aminothiazolo[4,5-*b*]pyridine-2-carboxamide (2b).** Yield 70%, m.p. >300 °C. MS, *m/z*: 350 $[M]^+$. ^{1}H NMR, δ: 4.83 (s, 2 H, NH_2); 6.77 (d, 1 H, pyridine, J = 8.8 Hz); 7.55 (m, 2 H, arom.); 7.67 (m, 2 H, arom.); 8.10 (d, 1 H, pyridine, J = 8.7 Hz); 9.39 (s, 1 H, NH). Found (%): C, 44.53; H, 2.85; Br, 22.60; N, 16.28; S, 9.03. $C_{13}H_9BrN_4OS$. Calculated (%): C, 44.71; H, 2.60; Br, 22.88; N, 16.04; S, 9.18.

***N*-(4-Chlorophenyl)-5-aminothiazolo[4,5-*b*]pyridine-2-carboxamide (2c).** Yield 82%, m.p. >300 °C. MS, *m/z*: 304 $[M]^+$. ^{1}H NMR, δ: 6.50 (s, 2 H, NH_2); 6.75 (d, 1 H, pyridine, J = 8.6 Hz); 7.43 (d, 2 H, arom., J = 8.3 Hz); 7.98 (d, 2 H, arom., J = 8.4 Hz); 8.21 (d, 1 H, pyridine, J = 8.5 Hz); 11.15 (s, 1 H, NH). Found (%): C, 51.30; H, 2.89; Cl, 11.68; N, 18.28; S, 10.57. $C_{13}H_9ClN_4OS$. Calculated (%): C, 51.24; H, 2.98; Cl, 11.63; N, 18.38; S, 10.52.

***N*-(4-Fluorophenyl)-5-aminothiazolo[4,5-*b*]pyridine-2-carboxamide (2d).** Yield 80%, m.p. >300 °C. MS, *m/z*: 288 $[M]^+$. ^{1}H NMR, δ: 6.50 (s, 2 H, NH_2); 6.79 (d, 1 H, pyridine, J = 8.1 Hz); 7.22 (m, 2 H, arom.); 7.95 (m, 2 H, arom.); 8.25 (d, 1 H, pyridine, J = 8.5 Hz); 11.05 (s, 1 H, NH). Found (%): C, 54.20; H, 3.19; F, 6.68; N, 19.37; S, 11.27. $C_{13}H_9FN_4OS$. Calculated (%): C, 54.16; H, 3.15; F, 6.59; N, 19.43; S, 11.12.

***N*-Pyridylthiooxamic acids (4, 6) (general procedure).** Solutions of monothiooxamides (**3** or **5**) in NaOH were oxidized with $K_3Fe(CN)_6$ as described above. The solutions were acidified with HCl and the precipitates that formed were filtered off, washed with water, dried, and recrystallized from 95% EtOH.

***N*-(4-Pyridyl)thiooxamic acid (4).** Yield 63%, m.p. 162—164 °C. MS, *m/z*: 182 $[M]^+$. ^{1}H NMR, δ: 4.12 (s, 1 H, OH); 6.50 (d, 2 H, J = 5.4 Hz); 8.22 (d, 2 H, J = 5.3 Hz). Found (%): C, 46.30; H, 3.45; N, 15.28; S, 17.23. $C_7H_6N_2O_2S$. Calculated (%): C, 46.15; H, 3.32; N, 15.37; S, 17.60.

***N*-(6-Methyl-2-pyridyl)thiooxamic acid (6).** Yield 65%, m.p. 156—158 °C. MS, *m/z*: 196 $[M]^+$. ^{1}H NMR, δ: 2.38 (s, 3 H, Me); 6.95 (d, 1 H, J = 7.9 Hz); 7.10 (d, 1 H, J = 7.5 Hz); 7.70 (d, 1 H, J = 7.7 Hz); 12.69 (s, 1 H, NH). Found (%): C, 48.64; H, 4.25; N, 14.18; S, 16.23. $C_8H_8N_2O_2S$. Calculated (%): C, 48.97; H, 4.11; N, 14.28; S, 16.34.

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