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One-step synthesis of 3-cyano-6-methyl-4-thienyl-5,6,7,8-tetrahydro[1,6]naphthyridine-2(1*H*)-thiones and annelated heterocyclic systems on their basis

A. A. Shestopalov, A. V. Gromova, L. A. Rodinovskaya, K. G. Nikishin, V. P. Litvinov, and A. M. Shestopalov★

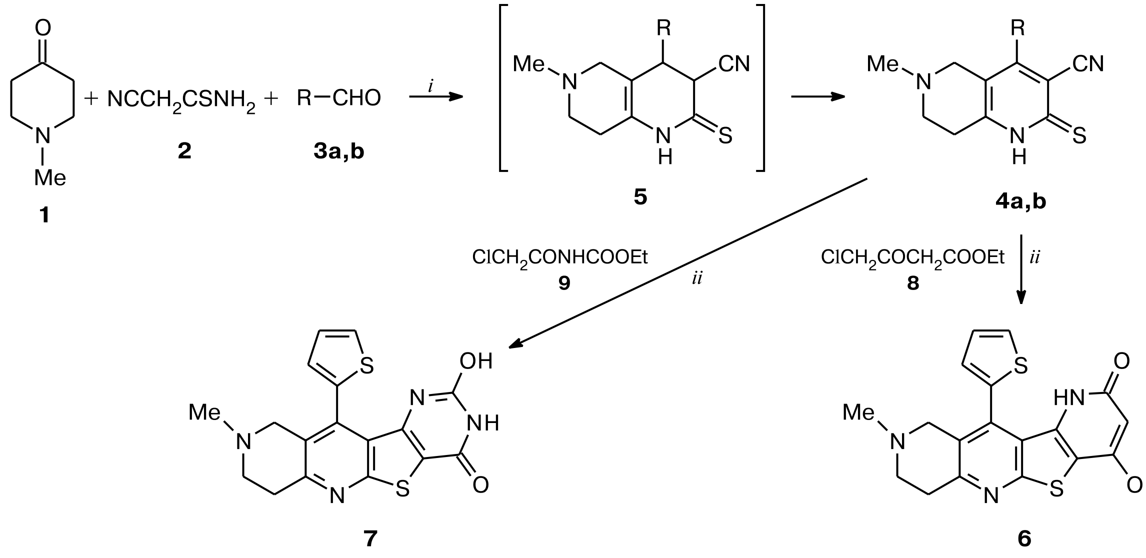
N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences,
47 Leninsky prosp., 119991 Moscow, Russian Federation.
Fax: +7 (095) 135 5328. E-mail: shchem@dol.ru

A broad spectrum of biological activity of substituted naphthyridines (from drugs to chemicals for plant protection) gives impetus to a search for routes to these compounds.[1] Naphthyridines containing vicinal cyano and thiol groups, which are widely used to obtain naphthyridines annelated with other heterocycles, are of great synthetic potential.[1,2]

In this communication, one-step synthesis of substituted 3-cyano-5,6,7,8-tetrahydro[1,6]naphthyridine-2(1*H*)-thiones and new polyannelated heterocycles on their basis is presented. The Et_3N-catalyzed multicomponent reaction of 1-methylpiperidin-4-one (**1**), cyanothioacetamide (**2**), thiophenecarboxaldehydes **3a,b**, and sodium thiosulfate in boiling ethanol for a short time yielded naphthyridines **4**. Sodium thiosulfate was used as a dehydrogenating agent for intermediate hydrogenated naphthyridines **5**, which increases the yields of naphthyridines **4** to 60—63%. Earlier, $Na_2S_2O_3$ was employed as an oxidant of intermediate substituted amino-4,5-dihydrothiophenes into aminothiophenes.[3] Unlike other oxidants (bromine or hydrogen peroxide) used to oxidize hydrogenated pyridine-2(1*H*)-thiones,[2] $Na_2S_2O_3$ does not oxidize pyridine-2(1*H*)-thiones into the corresponding bis(2-pyridyl) disulfides.

Naphthyridines **4** are convenient reagents in cascade reactions[1,4] used in the synthesis of polyannelated heterocycles **6** and **7**. The reaction of naphthyridine **4a** with ethyl 4-chloroacetoacetate **8** in boiling EtOH in the presence of EtONa gave pyrido[2´,3´:4,5]thieno[2,3-*b*][1,6]naphthyridine **6**. Under analogous conditions, the reaction of compound **4a** with chloroacetylurethan **9** afforded pyrimido[4´,5´:4,5]thieno[2,3-*b*][1,6]naphthyridine **7**, which represents an earlier unknown heterocyclic system.

^1H NMR spectra were recorded on a Bruker AM-300 spectrometer (300 MHz) in DMSO-d_6 with Me_4Si as the internal



3, 5: R = 2-thienyl (**a**), 3-thienyl (**b**).

Reagents and conditions: *i*. EtOH, Et_3N, $Na_2S_2O_3 \cdot 5\ H_2O$, Δ, 0.5 h; *ii*. 1) 2.5 *M* EtONa, EtOH, Δ, 0.5 h; 2) 10% HCl.

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standard. IR spectra were recorded on a Perkin-Elmer-577 instrument (KBr pellets). Elemental analysis was performed with a Perkin-Elmer C, H, N-analyzer.

3-Cyano-6-methyl-4-(2-thienyl)-5,6,7,8-tetrahydro[1,6]naphthyridine-2(1*H*)-thione (4a). A mixture of 1-methylpiperidin-4-one (**1**) (0.57 g, 5 mmol), cyanothioacetamide (**2**) (0.50 g, 5 mmol), thiophene-2-carboxaldehyde (**3a**) (0.56 g, 5 mmol), $Na_2S_2O_3 \cdot 5H_2O$ (1.90 g, 7.5 mmol), and Et_3N (0.3 mL, 2 mmol) in 30 mL of anhydrous ethanol was refluxed for 0.5 h. The reaction mixture was kept at 4 °C for 12 h, diluted with water (5 mL), and acidified with 10% HCl (0.3 mL). The precipitate that formed was filtered off and washed with ethanol and hexane to give compound **4a** (0.92 g, 64%) as small orange crystals, m.p. 259—263 °C (decomp.) (from nitromethane). Found (%): C, 58.24; H, 4.37; N, 14.25. $C_{14}H_{13}N_3S_2$. Calculated (%): C, 58.51; H, 4.56; N, 14.62. IR, n/cm^{-1}: 2228 (CN); 1202 (CS). ^{1}H NMR, d: 2.27 (s, 3 H, Me); 2.64 (m, 2 H, C(8)H_2); 2.88 (m, 2 H, C(7)H_2); 3.11 (s, 2 H, C(5)H_2); 7.24 (dd, 1 H, C(4´)H-thiophene, *J* = 3.3 Hz, *J* = 4.6 Hz); 7.33 (d, 1 H, C(5´)H-thiophene, *J* = 3.3 Hz); 7.86 (d, 1 H, C(3´)H-thiophene, *J* = 4.6 Hz); 13.92 (s, 1 H, NH).

3-Cyano-6-methyl-4-(3-thienyl)-5,6,7,8-tetrahydro[1,6]naphthyridine-2(1*H*)-thione (4b) was obtained analogously from thiophene-3-carboxaldehyde (**3b**) in 60% yield; orange crystals, m.p. 255—258 °C (decomp.) (from nitromethane). Found (%): C, 58.75; H, 4.18; N, 14.56. $C_{14}H_{13}N_3S_2$. Calculated (%): C, 58.51; H, 4.56; N, 14.62. IR, ν/cm^{-1}: 2220 (CN); 1208 (CS). ^{1}H NMR, δ: 2.24 (s, 3 H, Me); 2.63 (m, 2 H, C(8)H_2); 2.86 (m, 2 H, C(7)H_2); 3.03 (s, 2 H, C(5)H_2); 7.23 (d, 1 H, C(4´)H-thiophene, *J* = 4.3 Hz); 7.75 (d, 1 H, C(5´)H-thiophene, *J* = 4.3 Hz); 7.84 (s, 1 H, C(2´)H-thiophene); 13.87 (s, 1 H, NH).

4-Hydroxy-9-methyl-11-(2-thienyl)-7,8,9,10-tetrahydropyrido[2´,3´:4,5]thieno[2,3-*b*][1,6]naphthyridin-2(1*H*)-one (6). A solution of EtONa prepared from metallic sodium (0.11 g, 5 mmol) and EtOH (10 mL) was added to a mixture of compound **4a** (0.57 g, 2 mmol) and ethyl 4-chloroacetoacetate **8** (0.33 g, 2 mmol) in 25 mL of anhydrous ethanol. The stirred reaction mixture was refluxed for 0.5 h, cooled to 25 °C, and acidified with 10% HCl (3 mL). The precipitate that formed was filtered off to give a colorless powder (0.65 g, 88%), m.p. > 300 °C (from dioxane). Found (%): C, 58.18; H, 3.72; N, 11.08. $C_{18}H_{15}N_3O_2S_2$. Calculated (%): C, 58.52; H, 4.09; N, 11.37. IR, ν/cm^{-1}: 3410 (OH); 1625 (CONH). ^{1}H NMR, δ: 2.84 (s, 3 H, Me); 3.38 (m, 2 H, C(8)H_2); 3.47 (m, 2 H, C(7)H_2); 4.16 (s, 2 H, C(5)H_2); 6.05 (s, 1 H, C(3)H); 7.04 (d, 1 H, C(3´)H-thiophene, *J* = 3.2 Hz); 7.42 (dd, 1 H, C(4´)H-thiophene, *J* = 3.2 Hz, *J* = 5.5 Hz); 8.15 (d, 1 H, C(5´)H-thiophene, *J* = 5.5 Hz); 11.94 (s, 1 H, NH).

2-Hydroxy-9-methyl-11-(2-thienyl)-7,8,9,10-tetrahydropyrimido[4´,5´:4,5]thieno[2,3-*b*][1,6]naphthyridin-4(3*H*)-one (7) was obtained analogously from naphthyridine **4a** and chloroacetylurethan **9** in 82% yield; colorless powder, m.p. > 300 °C (from dioxane). Found (%): C, 54.82; H, 3.56; N, 14.87. $C_{17}H_{14}N_4O_2S_2$. Calculated (%): C, 55.12; H, 3.81; N, 15.12. IR, ν/cm^{-1}: 3508 (OH); 1642, 1704 (CONH). ^{1}H NMR, δ: 2.84 (s, 3 H, Me); 3.43 (m, 2 H, C(8)H_2); 3.53 (m, 2 H, C(7)H_2); 4.18 (s, 2 H, C(5)H_2); 7.00 (d, 1 H, C(3´)H-thiophene, *J* = 3.3 Hz); 7.43 (s, 1 H, OH); 7.45 (dd, 1 H, C(4´)H-thiophene, *J* = 3.3 Hz, *J* = 4.6 Hz); 8.15 (d, 1 H, C(5´)H-thiophene, *J* = 4.6 Hz); 11.58 (s, 1 H, NH).

References

1. V. P. Litvinov, *Usp. Khim.*, 2003, **71**, 75 [*Russ. Chem. Rev.*, 2003, **71** (Engl. Transl.)].
2. V. P. Litvinov, L. A. Rodinovskaya, Yu. A. Sharanin, A. M. Shestopalov, and A. Senning, *Sulfur Reports*, 1992, **13**, 1.
3. R. A. Rodinovskaya, A. M. Shestopalov, and K. S. Chunikhin, *Tetrahedron*, 2002, **58**, 4273.
4. V. A. Artyomov, L. A. Rodinovskaya, A. M. Shestopalov, and V. P. Litvinov, *Tetrahedron*, 1996, **52**, 1011.

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