Synthesis of thieno[2,3-*d*]pyrimidine and quinazoline derivatives from monothiooxamides ✾

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

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: zavi@ioc.ac.ru

A method for syntheses of previously unknown derivatives of thieno[2,3-*d*]pyrimidines and quinazolines from monothiooxamides was proposed.

Key words: ethyl 2-aminothiophene-3-carboxylate, methyl anthranylate, monothiooxamides, thieno[2,3-*d*]pyrimidines, quinazolines.

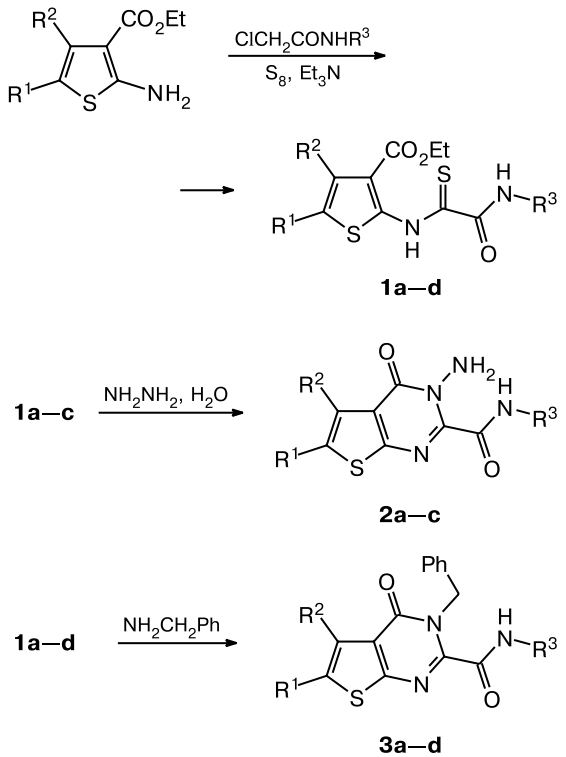
Heterocyclic compounds containing the amide function are rather widely used in syntheses of biologically active compounds.[1,2] We have previously developed a simple method for the synthesis of monothiooxamides[3] by the reaction of amino compounds with chloroacetamides and sulfur (as a solution in DMF). They are shown to be convenient starting compounds in syntheses of different heterocycles with the carbamoyl substituent, such as carbamoylimidazolines,[4] carbamoyl-1,2,4-oxadiazoles,[5] carbamoyl-1,3,4-oxadiazoles,[6] biscarbamoylfuroxanes,[6] and carbamoyl-1,2,4-triazoles.[7] We also found that the oxidation of the compounds, whose monothiooxamide fragments are bound to the phenyl ring or heterocycles, affords the fused compounds in high yields. Carbamoylbenzothiazoles[8] and carbamoylthieno[3,2-*d*]- and [2,3-*d*]thiazoles[9,10] were thus synthesized.

Note that the presence, in a heterocyclic compound, of a functional group that can react with the monothiooxamide fragment expands substantially the possibilities for the modification of these compounds owing to both intramolecular ring closure and introduction of an "external" reactant.

We used this approach for the syntheses of previously unknown thieno[2,3-*d*]pyrimidine and quinazoline derivatives from compounds containing vicinal ester and monothiooxamide groups. Pyrimidine systems are known to possess a wide spectrum of biological activity.[11—14]

The starting monothiooxamides of the thiophene series (**1a—d**) were synthesized by a previously published procedure[3] from substituted ethyl 2-aminothiophene-3-carboxylates. The reactions of compounds **1a—c** with hydrazine hydrate in ethanol afforded aminothienopyrimidines **2a—c** in 55—60% yields (Scheme 1). The reactions with benzylamine yielded benzylthienopyrimidines **3a—d** in almost the same yields (see Scheme 1). Monothiooxamide **4** was synthesized[3] from methyl anthranylate (Scheme 2). Its reactions with phenylhydr-

Scheme 1



1—3: R^1= Et, R^2 = H, R^3 =H (**a**), Ph (**b**), 4-ClC_6H_4 (**c**); R^1 = H, R^2 = Ph, R^3 = H (**d**)

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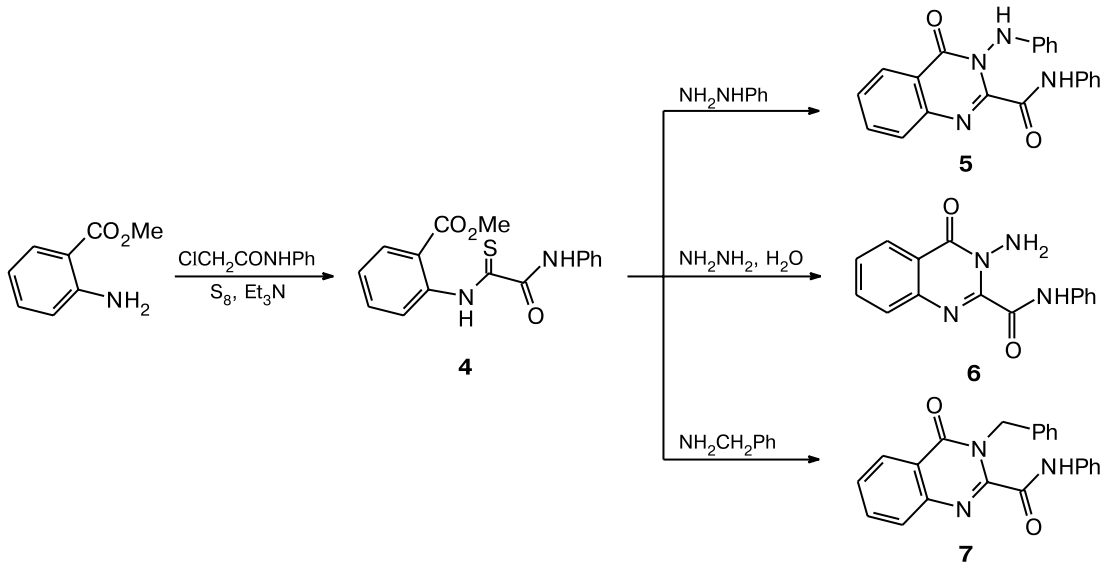
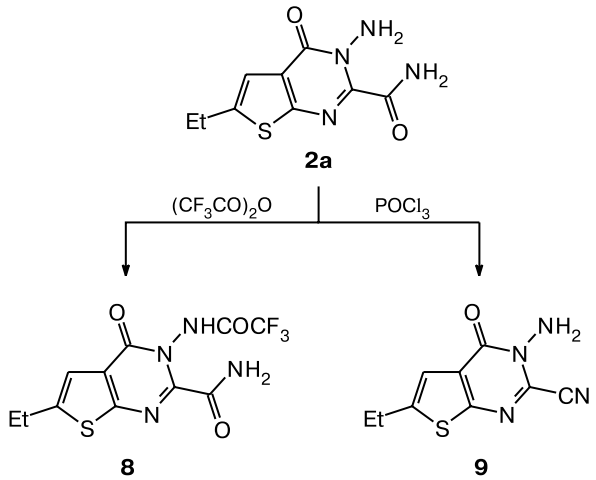
Scheme 2



azine, hydrazine hydrate, and benzylamine gave quinazoline derivatives **5—7**.

Trifluoroacetylation of compound **2a** affords derivative **8**, and its reaction with $POCl_3$ produces nitrile **9** (Scheme 3).

Scheme 3



The structures of the synthesized compounds were confirmed by the data from elemental analysis, mass spectrometry, and ^{1}H NMR spectroscopy. The mass spectra of all compounds contain peaks of molecular ions. The ^{1}H NMR spectra exhibit signals of protons of the thiophene ring (δ 7.20—7.30) and amino group (δ 7.10—7.20) along with signals of the ethyl group and aromatic ring.

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 obtained on a Kratos instrument with direct inlet of samples into the ion source with an ionization energy of 70 eV and a controlling voltage of 1.75 kV. Commercial reagents (Acros) were used. Monothiooxamides **1a—d** and **4** were synthesized by a previously described procedure[3] and used without additional purification.

3-Amino-2-carbamoylthienopyrimidines (2a—c) and 3-amino-2-carbamoylquinazoline 6 (general procedure). A solution of the corresponding monothiooxamide **1a—d** (1.6 mmol) or **4** (0.5 g, 1.6 mmol) and hydrazine hydrate (0.16 g, 3.1 mmol) in ethanol (7 mL) was refluxed for 3 h. After cooling, the solvent was evaporated, and a small amount of Et_2O was added to the residue. The precipitate that formed was filtered off, dried, and crystallized from ethanol.

3-Amino-6-ethyl-4-oxo-3,4-dihydrothieno[2,3-*d*]pyrimidine-2-carboxamide (2a). The yield was 61%, m.p. 174—176°C. MS, *m/z*: 238 $[M]^+$. ^{1}H NMR, δ: 1.38 (t, 3 H, Me, J = 7.4 Hz); 2.92 (q, 2 H, CH_2); 5.90 (s, 1 H, $CONH_2$); 7.10 (s, 2 H, NH_2); 7.20 (s, 1 H, thiophene); 7.58 (s, 1 H, $CONH_2$). Found (%): C, 45.20; H, 4.35; N, 23.50; S, 13.38. $C_9H_{10}N_4O_2S$. Calculated (%): C, 45.38; H, 4.20; N, 23.53; S, 13.45.

3-Amino-6-ethyl-4-oxo-3,4-dihydrothieno[2,3-*d*]pyrimidine-2-carboxanilide (2b). The yield was 55%, m.p. 125—127 °C. MS, *m/z*: 314 $[M]^+$. ^{1}H NMR, δ: 1.40 (t, 3 H, CH_3, J = 7.4 Hz); 2.95 (q, 2 H, CH_2); 7.20 (s, 1 H, thiophene + 2 H, NH_2); 7.40 (m, 3 H, arom.); 7.70 (s, 2 H, arom., J = 7.9 Hz); 9.58 (s, 1 H, NH). Found (%): C, 57.28; H, 4.50; N, 17.95; S, 10.10. $C_{15}H_{14}N_4O_2S$. Calculated (%): C, 57.32; H, 4.46; N, 17.83; S, 10.19.

***N*-(4-Chlorophenyl)-3-amino-6-ethyl-4-oxo-3,4-dihydrothieno[2,3-*d*]pyrimidine-2-carboxamide (2c).** The yield was 60%, m.p. 178—180 °C. MS, *m/z*: 348 $[M]^+$. ^{1}H NMR, δ: 1.45 (t, 3 H,

Me, J = 7.4 Hz); 2.95 (q, 2 H, CH_2); 7.20 (s, 1 H, thiophene + + 2 H, NH_2); 7.40 (d, 2 H, arom., J = 8.6 Hz); 7.70 (d, 2 H, arom., J = 8.6 Hz); 9.60 (s, 1 H, NH). Found (%): C, 51.60; H, 3.88; Cl, 10.11; N, 16.10; S, 9.25. $C_{15}H_{13}ClN_4O_2S$. Calculated (%): C, 51.65; H, 3.73; Cl, 10.19; N, 16.07; S, 9.18.

3-Amino-4-oxo-3,4-dihydroquinazolinone-2-carboxanilide (6). The yield was 50%, m.p. 163—165 °C. MS, m/z: 280 $[M]^+$. ^1H NMR, δ: 5.80 (s, 2 H, NH_2); 7.15 (d, 1 H, arom., J = 6.7 Hz); 7.40 (m, 2 H, arom.); 7.68 (m, 3 H, arom.); 7.79 (d, 1 H, arom., J = 7.9 Hz); 7.90 (d, 1 H, arom., J = 7.2 Hz); 8.22 (d, 1 H, arom., J = 7.6 Hz). Found (%): C, 64.40; H, 4.80; N, 20.15. $C_{22}H_{17}N_3O_2$. Calculated (%): C, 64.29; H, 4.29; N, 20.00.

3-Benzyl-2-carbamoylthienopyrimidines (3a—d) and 3-benzyl-2-carbamoylquinazoline 7 (general procedure). A mixture of monothiooxamide **1a—d** (1.1 mmol) or **4** (0.34 g, 1.1 mmol) and benzylamine (2 mL, 18.3 mmol) was boiled until hydrogen sulfide evolution ceased (20 min). After cooling, diethyl ether was added to the reaction mixture, and the resulting solution was washed with 1% HCl. The organic layer was dried, the solvent was evaporated, and small amount of diethyl ether was added to the residue. The precipitate that formed was filtered off, dried, and crystallized from ethanol.

3-Benzyl-6-ethyl-4-oxo-3,4-dihydrothieno[2,3-*d*]pyrimidine-2-carboxamide (3a). The yield was 53%, m.p. 173—175 °C. MS, m/z: 313 $[M]^+$. ^1H NMR, δ: 1.38 (t, 3 H, Me, J = 7.4 Hz); 2.92 (q, 2 H, CH_2); 5.65 (s, 1 H, $CONH_2$); 5.85 (s, 2 H, CH_2); 7.25 (m, 5 H, arom.; 1 H, thiophene; 1 H, $CONH_2$). Found (%): C, 61.25; H, 4.81; N, 13.49; S, 10.10. $C_{16}H_{15}N_3O_2S$. Calculated (%): C, 61.34; H, 4.79; N, 13.42; S, 10.22.

3-Benzyl-6-ethyl-4-oxo-3,4-dihydrothieno[2,3-*d*]pyrimidine-2-carboxanilide (3b). The yield was 61%, m.p. 173—175 °C. MS, m/z: 389 $[M]^+$. ^1H NMR, δ: 1.40 (t, 3 H, Me, J = 7.4 Hz); 2.95 (q, 2 H, CH_2); 6.08 (s, 2 H, CH_2); 7.30 (m, 1 H, thiophene + +10 H, arom.); 9.28 (s, 1 H, NH). Found (%): C, 67.76; H, 4.98; N, 10.87; S, 8.12. $C_{22}H_{19}N_3O_2S$. Calculated (%): C, 67.87; H, 4.88; N, 10.80; S, 8.23.

***N*-(4-Chlorophenyl)-3-benzyl-6-ethyl-4-oxo-3,4-dihydrothieno[2,3-*d*]pyrimidine-2-carboxamide (3c).** The yield was 50%, m.p. 183—185 °C. MS, m/z: 423 $[M]^+$. ^1H NMR, δ: 1.40 (t, 3 H, Me, J = 7.4 Hz); 2.95 (q, 2 H, CH_2); 6.05 (s, 2 H, CH_2); 7.30 (m, 1 H, thiophene + 9 H, arom.); 9.28 (s, 1 H, NH). Found (%): C, 62.21; H, 4.31; N, 9.86; S, 7.69; Cl, 8.30. $C_{22}H_{18}ClN_3O_2S$. Calculated (%): C, 62.34; H, 4.25; N, 9.92; S, 7.56; Cl, 8.38.

3-Benzyl-4-oxo-5-phenyl-3,4-dihydrothieno[2,3-*d*]pyrimidine-2-carboxamide (3d). The yield was 45%, m.p. 185—187 °C. MS, m/z: 361 $[M]^+$. ^1H NMR, δ: 5.42 (s, 2 H, CH_2); 7.25 (m, 5 H, arom.); 7.38 (m, 3 H, arom.); 7.50 (d, 2 H, arom., J = 6.1 Hz); 7.65 (s, 1 H, thiophene); 8.10 (s, 1 H, NH_2); 8.43 (s, 1 H, NH_2). Found (%): C, 66.42; H, 4.20; N, 11.73; S, 8.77. $C_{20}H_{15}N_3O_2S$. Calculated (%): C, 66.48; H, 4.16; N, 11.63; S, 8.86.

3-Benzyl-4-oxo-3,4-dihydroquinazoline-2-carboxanilide (7). The yield was 75%, m.p. 165—166 °C. MS, m/z: 355 $[M]^+$. ^1H NMR, δ: 5.45 (s, 2 H, CH_2); 7.28 (m, 5 H, arom.); 7.39 (m, 3 H, arom.); 7.65 (m, 3 H, arom.); 7.90 (m, 2 H, arom.); 8.21 (d, 1 H, arom., J = 7.8 Hz); 10.89 (s, 1 H, NH). Found (%): C, 74.30; H, 4.84; N, 11.89. $C_{22}H_{17}N_3O_2$. Calculated (%): C, 74.37; H, 4.79; N, 11.83.

3-Anilino-4-oxo-3,4-dihydroquinazoline-2-carboxanilide (5). A mixture of monothiooxamide **4** (0.5 g, 1.6 mmol) and phenylhydrazine (0.25 g, 2.3 mmol) in ethanol (5 mL) was refluxed for 5 days. After cooling, the precipitate that formed was filtered off, dried, and recrystallized from ethanol. The yield was 61%, m.p. 210—212 °C. MS, m/z: 356 $[M]^+$. ^1H NMR, δ: 6.85 (m, 2 H, arom.); 7.18 (m, 3 H, arom.); 7.35 (m, 2 H, arom.); 7.62 (m, 3 H, arom.); 7.90 (m, 2 H, arom.); 8.20 (d, 2 H, arom., J = 7.9 Hz); 9.17 (s, 1 H, NH); 10.89 (s, 1 H, NH). Found (%): C, 70.71; H, 4.53; N, 15.63. $C_{21}H_{16}N_4O_2$. Calculated (%): C, 70.79; H, 4.49; N, 15.73.

6-Ethyl-3-(trifluoroacetamido)-4-oxo-3,4-dihydrothieno[2,3-*d*]pyrimidine-2-carboxamide (8). A mixture of compound **2a** (0.24 g, 1.0 mmol) and $(CF_3CO)_2O$ (10 mL) was stirred for 2 h at ~20 °C and then concentrated. The precipitate that formed was recrystallized from ethanol. The yield was 75%, m.p. 222—224 °C. MS, m/z: 334 $[M]^+$. ^1H NMR, δ: 1.35 (t, 3 H, CH_3, J = 7.4 Hz); 2.95 (q, 2 H, CH_2); 7.10 (s, 2 H, NH_2); 7.29 (s, 1 H, thiophene); 8.10 (s, 1 H, $CONH_2$); 8.45 (s, 1 H, $CONH_2$). Found (%): C, 39.47; H, 2.73; F, 17.02; N, 16.65; S, 9.50. $C_{11}H_9F_3N_4O_3S$. Calculated (%): C, 39.52; H, 2.69; F, 17.07; N, 16.77; S, 9.58.

3-Amino-6-ethyl-4-oxo-3,4-dihydrothieno[2,3-*d*]pyrimidine-2-carbonitrile (9). $POCl_3$ (10 mL) was added to compound **2a** (0.24 g, 1.0 mmol), and the mixture was refluxed for 1 h; $POCl_3$ was distilled off, and ice was added to the residue. The precipitate that formed was filtered off and recrystallized from ethanol. The yield was 41%, m.p. >300 °C. MS, m/z: 220 $[M]^+$. ^1H NMR, δ: 1.30 (t, 3 H, CH_3, J = 7.4 Hz); 2.95 (q, 2 H, CH_2); 6.05 (s, 2 H, NH_2); 7.30 (s, 1 H, thiophene). Found (%): C, 49.18; H, 3.75; N, 25.50; S, 14.43. $C_9H_8N_4OS$. Calculated (%): C, 49.09; H, 3.64; N, 25.45; S, 14.55.

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