New method for the synthesis of substituted thieno[3,2-*b*]pyridines and 5*H*-pyrano[2,3-*d*]thieno[3,2-*b*]pyridines derived from them

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A new highly selective method was developed for the synthesis of substituted thieno[3,2-*b*]-pyridines based on the domino reaction of monopotassium salt (rather than dipotassium one) of carbamoylcyanodithioacetic acid with ethyl 4-chloroacetoacetate. Substituted 5*H*-pyrano[2,3-*d*]-thieno[3,2-*b*]pyridines were synthesized based on these thieno[3,2-*b*]pyridines.

Key words: thieno[3,2-*b*]pyridines, N-substituted cyanoacetamides, potassium cyanoethanedithioate, domino reactions, ethyl 4-chloroacetoacetate, 2-amino-3-cyanopyrans, multicomponent condensation.

Substituted thieno[3,2-*b*]pyridines possess pronounced biological activity. Among them were found ligands of γ-aminobutyric acid receptors,[1] immunomodulators,[1,2] calcium channel inhibitors,[1,3] and herbicides.[1] Lately, an interest grows to thiophenes containing an N-substituted amide group at position 3.[4] Among these compounds, including those with annulated carbo- or heterocycles, are found ligands of cannabinoid receptors,[5] compounds inhibiting development of malignant tumors,[6] AMPA-receptor modulators,[7] antiplasmodium agents,[8] herbicides,[9] and agents used against breast cancer.[10]

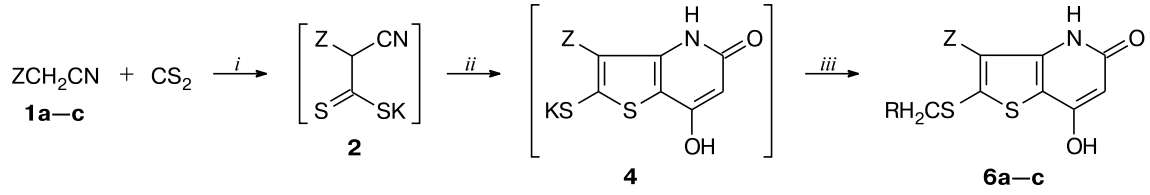
Earlier,[11] we have developed an approach to the synthesis of thieno[3,2-*b*]pyridines based on malononitrile and cyanoacetamide. A key step of this method consists in the generation in solution of the dipotassium salt of 2,2-dicyanoethenedithiol or its 2-carbamoyl analog. Its subsequent reaction with ethyl 4-chloroacetoacetate followed the domino reaction and led to a simultaneous closure of thiophene and pyridine rings.[11]

The present work is devoted to the development of a new highly selective method for the synthesis of such compounds based on the use of the monopotassium salt of substituted dithioacetic acids. N-Substituted cyanoacetamides were used as the starting compounds, that made it possible to obtain thieno[3,2-*b*]pyridines containing potentially pharmacophoric groups.

Results and Discussion

The synthesis was carried out by the domino reactions. Since the alkylation at one or both sulfur atoms of 2,2-dicyanoethenedithiol dipotassium salt is known to be nonselective[1,12] and results in the decreased yields of the target products, we developed an alternative approach (Scheme 1).

Scheme 1



Regents and conditions: *i*. KOH, EtOH, 10 °C; *ii*. 1) $ClCH_2COCH_2CO_2Et$ (**3**), 20 °C; 2) 2 KOH, EtOH, D; *iii*. $PhCH_2Cl$ (**5a**) or MeI (**5b**).

Regents	Z	R	Products
1a, 5a	$MeO(CH_2)_3NHCO$	Ph	**6a**
1b, 5b	*cyclo*-C_3H_5NHCO	H	**6b**
1c, 5b	$PhCH_2NHCO$	H	**6c**

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This approach is distinguished by the generation in solution of the monopotassium salt of carbamoylcyanodithioacetic acid (**2**) from cyanoacetic acid amides **1a—c** and carbon disulfide. Further alkylation of salt **2** with ethyl 4-chloroacetoacetate (**3**) proceeded highly regioselectively at one sulfur atom, rather than at both. To complete the domino reaction procedure, an excess of KOH in ethanol was added to the reaction mixture to run the consecutive Thorpe—Ziegler and Thorpe—Guareshi reactions (see Scheme 1). The thus obtained solution of thieno[3,2-*b*]-pyridine potassium salt **4** was treated with alkyl halides **5a**,**b**. Such a sequence of reactions increases the regioselectivity of the process and the yields (by 7—10%) of the final compounds **6a—c** as compared to the unsubstituted amides described earlier.[11]

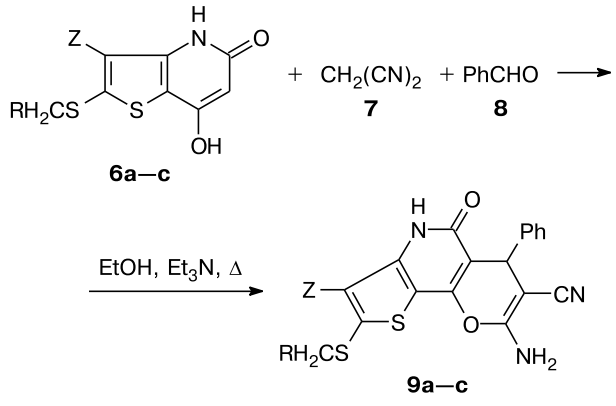
The following *N*-substituted cyanoacetamides were used as the starting compounds: *N*-(3-methoxypropyl)- (**1a**), *N*-cyclopropyl- (**1b**), and *N*-benzylcyanoacetamide (**1c**).

The structure of thienopyridines **6a—c** was confirmed by ^{1}H NMR and IR spectroscopy. The IR spectra of compounds **6** exhibit characteristic absorption bands of the NH bonds of the amide and pyridone groups in the region 3360—3260 cm^{-1} and the signals of the carbonyl groups in the region 1630 cm^{-1}.

The ^{1}H NMR spectra have the characteristic signals for the protons of the NH and OH groups, as well as the signal for the C(6)H proton at δ 6.01—6.06.

Compounds **6a—c** have several reactive centers and can be used for further synthesis as convenient building blocks. Thus, they give a three-component reaction with malononitrile (**7**) and benzaldehyde (**8**), which leads to the formation of annulated pyrans **9a—c** (Scheme 2), whose analogs possess high antitumor activity.[13]

Scheme 2



Regents	Z	R	Products
6a	$CH_3O(CH_2)_3NHCO$	Ph	**9a**
6b	*cyclo*-C_3H_5NHCO	H	**9b**
6c	$C_6H_5CH_2NHCO$	H	**9c**

The IR spectra of compounds **9a—c** exhibit absorption bands of the NH_2 and NH groups in the region 3400—3200 cm^{-1}, the nitrile group at 2200—2180 cm^{-1}, and the carbonyl groups at 1670 and 1630 cm^{-1}. The presence of the signal for the proton at atom C(6) as a singlet in the region δ 4.5—4.6 is characteristic of the ^{1}H NMR spectra of compounds **9**.

In conclusion, we developed a new highly selective method for the synthesis of substituted thieno[3,2-*b*]-pyridines. This method is based on the generation of the monopotassium salt of *N*-substituted carbamoylcyanodithioacetic acids and its reaction with ethyl 4-chloroacetoacetate following the domino reaction. The thieno-[3,2-*b*]pyridines obtained were used to synthesize substituted 5*H*-pyrano[2,3-*d*]thieno[3,2-*b*]pyridines.

Experimental

Melting points were determined on a Kofler heating stand. IR spectra were recorded on a Bruker Alpha spectrophotometer in KBr pellets, ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM 300 spectrometer (300.13 and 75.47 MHz, respectively) in DMSO-d_6. *N*-substituted cyanoacetamides **1** were obtained from ethyl cyanoacetate and the corresponding amines according to the known method.[14]

Synthesis of substituted 5,7-dioxythieno[3,2-*b*]pyridines 6a—c (general procedure). A corresponding nitrile **1** (25 mmol) was added to a solution of KOH (1.4 g, 25 mmol) in EtOH (50 mL) at 10 °C, and the mixture was stirred until it dissolved. Carbon disulfide (1.5 mL, 25 mmol) was added to the solution obtained, which was stirred for 20 min. Then, H_2O (10—15 mL) was added to the reaction mixture until a precipitate formed was dissolved, followed by the addition of ester **3** (3.4 mL, 25 mmol) and stirring for 10 min. After this, a solution of KOH (2.8 g, 50 mmol) in EtOH (100 mL) was added, and the mixture was refluxed for 2.5 h. A dark red solution was cooled and, after addition of concentrated HBr (2.8 mL, 25 mmol), stirred for 30 min. A corresponding alkyl halide **5** (25 mmol) was added to the solution obtained, which was heated to boiling point and cooled. A precipitate formed was filtered off to obtain thieno[3,2-*b*]pyridines **6a—c** in 75—86% yields.

2-(Benzylthio)-*N*-(3-methoxypropyl)-5-oxo-7-oxy-4,5-dihydrothieno[3,2-*b*]pyridine-3-carboxamide (6a). The yield was 75%, m.p. 197—200 °C. IR, ν/cm^{-1}: 3364, 3332 (NH), 1624 (CO). ^{1}H NMR, δ: 1.79 (m, 2 H, $CH_2\underline{CH_2}CH_2OCH_3$); 3.24 (s, 3 H, OCH_3); 3.28—3.43 (m, 4 H, $\underline{CH_2}CH_2\underline{CH_2}OCH_3$); 4.33 (s, 2 H, SCH_2); 6.03 (s, 1 H, C(6)H); 7.25—7.40 (m, 3 H, C_6H_5, H(3, 4, 5)); 7.47 (m, 2 H, C_6H_5, H(2, 6)); 9.74 (br.s, 1 H, CONH); 10.79 (br.s, 1 H, OH); 11.67 (s, 1 H, N(4)H). ^{13}C NMR, δ: 29.38, 35.72, 38.02, 57.90, 69.78, 90.97, 112.17, 127.48, 128.52, 128.58, 129.10, 136.09, 160.35, 162.44, 163.74. The signals in the ^{13}C NMR spectrum partially overlap. Found (%): C, 56.19; H, 4.72; N, 6.64. $C_{19}H_{20}N_2O_4S_2$. Calculated (%): C, 56.42; H, 4.98; N, 6.93.

***N*-Cyclopropyl-2-methylthio-5-oxo-7-oxy-4,5-dihydrothieno[3,2-*b*]pyridine-3-carboxamide (6b).** The yield was 86%, m.p. 257—259 °C. IR, ν/cm^{-1}: 3356, 3260 (NH), 1632, 1616 (CO). ^{1}H NMR, δ: 0.58—0.78 (m, 4 H, $(\underline{CH_2})_2CH$); 2.55 (m, 3 H, SCH_3); 2.84 (m, 1 H, $(CH_2)_2\underline{CH}$); 6.01 (s, 1 H, C(6)H); 9.71

(br.s, 1 H, NH); 10.84 (br.s, 1 H, OH); 11.67 (br.s, 1 H, N(4)H). Found (%): C, 48.36; H, 3.85; N, 9,29. $C_{12}H_{12}N_2O_3S_2$. Calculated (%): C, 48.63; H, 4.08; N, 9,45.

***N*-Benzyl-2-methylthio-5-oxo-7-oxy-4,5-dihydrothieno-[3,2-*b*]pyridine-3-carboxamide (6c).** The yield was 76%, m.p. 272—275 °C. IR, ν/cm^{-1}: 3312, 3284 (NH), 1636, 1620 (CO). ^{1}H NMR, δ: 2.58 (s, 3 H, SCH_3); 4.56 (d, 2 H, $C_6H_5\underline{CH_2}NH$, J = 6.2 Hz); 6.06 (s, 1 H, C(6)H); 7.20—7.35 (m, 5 H, C_6H_5); 10.36 (br.s, 1 H, NH); 10.81 (br.s, 1 H, OH); 11.68 (br.s, 1 H, N(4)H). Found (%): C, 55.72; H, 3.84; N, 7.75. $C_{16}H_{14}N_2O_3S_2$. Calculated (%): C, 55.47; H, 4.07; N, 8.09.

Synthesis of substituted 8-amino-7-cyano-5-oxo-6-phenyl-4,6-dihydro-5*H*-pyrano[2,3-*d*]thieno[3,2-*b*]pyridines 9a—c (general procedure). A mixture of the corresponding thienopyridine **6** (5 mmol), malononitrile (0.33 g, 5 mmol), benzaldehyde (0.53 g, 5 mmol), and Et_3N (1 mL, 7 mmol) in EtOH (30 mL) was refluxed for 30 min and cooled. A precipitate formed was filtered off to obtain pyrans **9a—c** in 58—78% yields.

8-Amino-2-benzylthio-7-cyano-*N*-(3-methoxypropyl)-5-oxo-6-phenyl-4,6-dihydro-5*H*-pyrano[2,3-*d*]thieno[3,2-*b*]pyridine-3-carboxamide (9a). The yield was 58%, m.p. 158—160 °C. IR, ν/cm^{-1}: 3372, 3290, 3204 (NH_2, NH), 2196 (CN), 1668, 1624 (CO, C=C, δ, NH_2). ^{1}H NMR, δ: 1.76 (m, 2 H, $CH_2\underline{CH_2}CH_2OCH_3$); 3.20 (s, 3 H, OCH_3); 3.27—3.45 (m, 4 H, $\underline{CH_2}CH_2\underline{CH_2}OCH_3$); 4.36 (s, 2 H, SCH_2); 4.54 (s, 1 H, C(6)H); 7.05—7.5 (m, 12 H, 2 C_6H_5, NH_2); 9.35 (br.s, 1 H, CONH); 11.61 (br.s, 1 H, N(4)H). Found (%): C, 62.04; H, 4.83; N, 10.34. $C_{29}H_{26}N_4O_4S_2$. Calculated (%): C, 62.35; H, 4.69; N, 10.03.

8-Amino-7-cyano-*N*-cyclopropyl-2-methylthio-5-oxo-6-phenyl-4,6-dihydro-5*H*-pyrano[2,3-*d*]thieno[3,2-*b*]pyridine-3-carboxamide (9b). The yield was 66%, m.p. 302—304 °C. IR, ν/cm^{-1}: 3376, 3256, 3188 (NH_2, NH), 2188 (CN), 1660, 1620 (CO, C=C, δ, NH_2). ^{1}H NMR, δ: 0.55—0.71 (m, 4 H, $(\underline{CH_2})_2CH$); 2.62 (s, 3 H, SCH_3); 2.84 (m, 1 H, $(CH_2)_2\underline{CH}$); 4.57 (s, 1 H, C(6)H); 7.15—7.35 (m, 7 H, C_6H_5, NH_2); 9.41 (br.s, 1 H, CONH); 11.64 (s, 1 H, N(4)H). Found (%): C, 58.91; H, 3.86; N, 12.23. $C_{22}H_{18}N_4O_3S_2$. Calculated (%): C, 58.65; H, 4.03; N, 12.44.

8-Amino-*N*-benzyl-7-cyano-2-methylthio-5-oxo-6-phenyl-4,6-dihydro-5*H*-pyrano[2,3-*d*]thieno[3,2-*b*]pyridine-3-carboxamide (9c). The yield was 78%, m.p. 279—281 °C. IR, ν/cm^{-1}: 3544, 3480, 3312 (NH_2, NH), 2180 (CN), 1656, 1628 (CO, C=C, δ, NH_2). ^{1}H NMR, δ: 2.63 (s, 3 H, SCH_3); 4.45—4.60 (m, 3 H, C(6)H, CH_2); 7.12—7.35 (m, 12 H, 2 C_6H_5, NH_2); 10.07 (br.s, 1 H, CONH); 11.61 (br.s, 1 H, N(4)H). Found (%): C, 62.07; H, 3.84; N, 11.36. $C_{26}H_{20}N_4O_3S_2$. Calculated (%): C, 62.38; H, 4.03; N, 11.19.

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