Reactions of (*S*)-*N*-trifluoroacetyl-5-bromo-4-oxonorvaline methyl ester with vicinal mercaptonitriles. Synthesis of δ-hetaryl-substituted α-amino acids

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The reactions of (*S*)-*N*-trifluoroacetyl-5-bromo-4-oxonorvaline methyl ester with vicinal mercaptonitriles afforded δ-hetaryl-*N*-trifluoroacetyl-substituted α-amino acids (hetaryl is thiazol-2-yl, 2-thienyl, or thieno[2,3-*b*]pyridin-6-yl).

Key words: (*S*)-*N*-trifluoroacetyl-5-bromo-4-oxonorvaline methyl ester, vicinal mercaptonitriles, thiazole, thiophene, thieno[2,3-*b*]pyridine, Thorpe—Ziegler cyclization.

α-Amino acid derivatives containing the isoxazole, oxadiazolone, pyrimidinone, or triazolone fragments are considered as promising pharmaceuticals for therapy of central nervous system diseases (Alzheimer's disease, disseminated sclerosis, schizophrenia, epilepsy) and acquired immunodeficiency syndrome.[1] Hence, it was of interest to prepare such derivatives containing fragments of other heterocycles, in particular, thiophene and thiazole.

Starting from L-aspartic acid (**1**) we prepared (*S*)-*N*-trifluoroacetyl-5-bromo-4-oxonorvaline methyl ester (**2**)[2,3] and used the latter as key compound for the synthesis of the above-mentioned derivatives. Earlier,[3] the reactions of ester **2** with 1,3-dinucleophiles, such as 2-aminopyridine, 2-aminopyrimidine, 3-aminopyridazine, thiourea, or thiobenzamide, afforded optically active methyl 3-azaindolyl- and 3-(4-thiazolyl)-2-trifluoroacetylaminopropionates.

We studied the reactions of bromoketone **2** with vicinal mercaptonitriles, which were prepared from heterocumulenes (CS_2, PhNCS, KSCN) and nitriles (malononitrile, cyanamide) (Scheme 1).

The reaction of sodium 2,2-dicyanoethylene-1,1-dithiolate (**3**) with two equivalents of bromoketone **2** was carried out in two steps. Thiophene **4** formed in the first step is sufficiently stable to be isolated. The addition of a base and heating caused the second Thorpe—Ziegler cyclization to form thienothiophene **5**. The thiophene derivative bearing one amino acid residue can also be prepared based on bromoketone **2** and dithiolate **3**. For example, the successive reactions of compound **3** with an equimolar amount of MeI and then with compound **2** in aqueous MeOH gave rise to methylthio-substituted thiophene **6** (see Scheme 1).

The characteristic feature of the reaction of bromoketone **2** with compound **3** giving rise to thiophenes **4** or **6** is that their Thorpe—Ziegler reaction does not require the addition of an excess of a base, unlike analogous reactions of vicinal mercaptonitriles with α-halocarbonyl compounds.[4—6] Starting from phenyl isothiocyanate (**7**), malonodinitrile (**8**), and bromoketone **2**, we prepared compound **9** without isolation of intermediate 2,2-dicyano-1-phenylaminoethylene-1-thiolate **10**. We synthesized thiazole **12** by an analogous reaction with the use of cyanamide (**11**) instead of malononitrile.

Another approach was employed in the reaction of rhodanide **13**, which was prepared from bromoketone **2** and KSCN, with malononitrile **8** in the presence of KOH. In this case, the ring closure proceeded as Hantzsch rather than Thorpe—Ziegler cyclization. Intramolecular condensation involving the carbonyl and amino groups of adduct **14** afforded thiazolyl acid ester **15**. Earlier, an analogous transformation has been investigated in the reaction of compound **2** with thiourea.[3]

We used the reactions of compound **2** with 3-cyano-1*H*-pyridine-2-thiones **16a—p** for the synthesis of compounds **17a—f** and **18a—n** containing the pyridine ring. The results of the reactions of bromoketone **2** with compounds **16a—p** depend on the amount of the base added. In the presence of an equimolar amount of KOH, the reaction proceeded as the bimolecular nucleophilic substitution to form pyridines **17a—f** (Scheme 2). The reactions of pyridine-2(1*H*)-thiones with optically active methyl 2-bromopropionate proceeded analogously. These reactions were accompanied by the Walden inversion, which indicates that the reactions proceeded by the S_N2 mechanism.[4]

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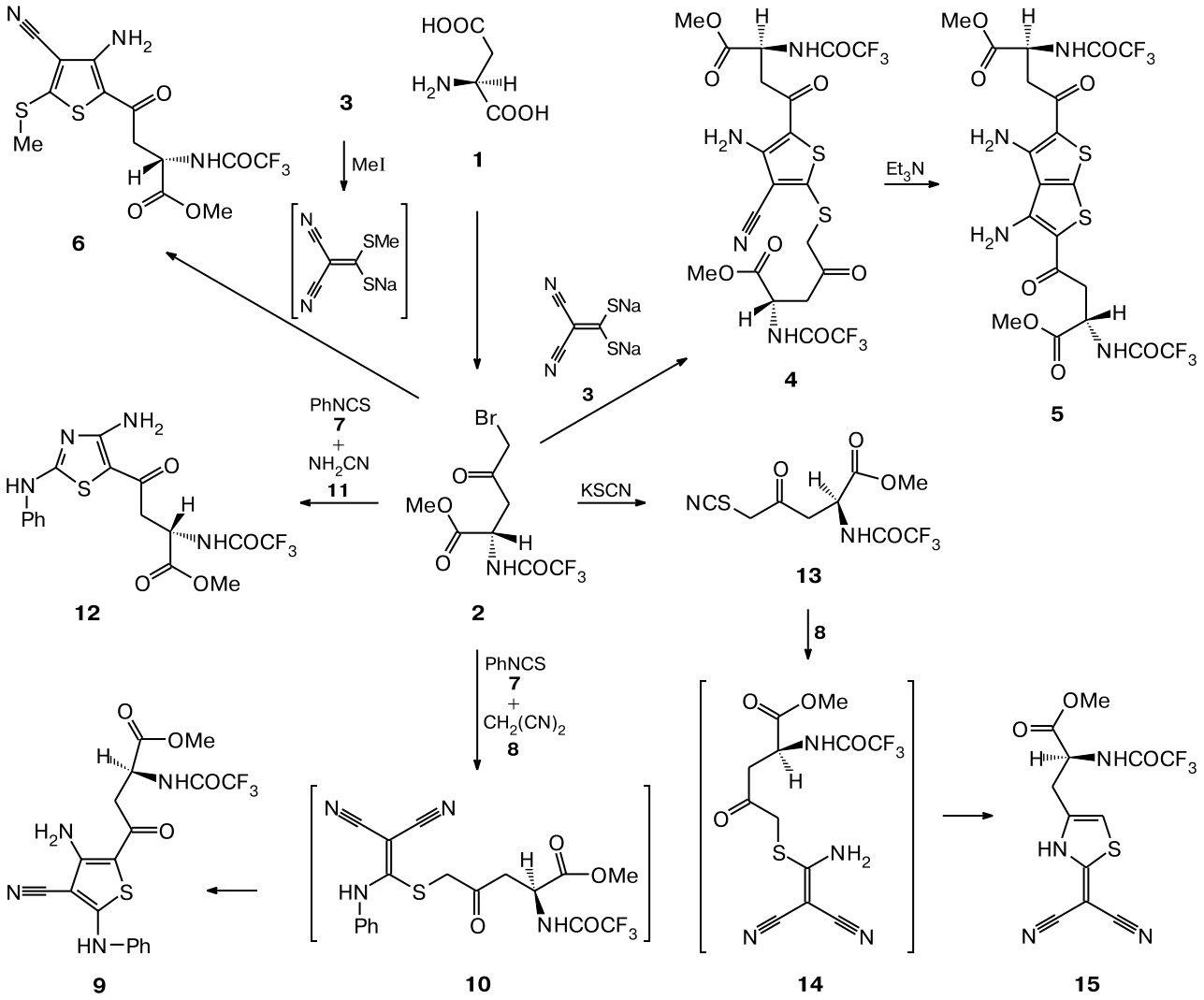
Scheme 1



In the presence of an excess of a base, pyridines **17** were transformed into 3-aminothieno[2,3-*b*]pyridines **18a—n** (method *A*). The latter were also prepared from pyridinethiones **16a—o** upon heating with bromide **2** in MeOH in the presence of MeONa (method *B*). Hence, the synthesis of compounds **18** can be represented as a sequence of successive reactions involving the bimolecular nucleophilic substitution and Thorpe—Ziegler cyclization.

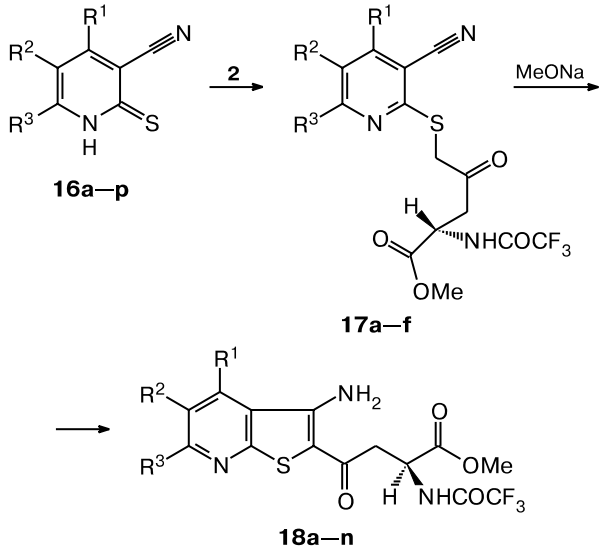
Compound **2** can be used also in the synthesis of thienopyrimidines. The reaction of 2-amino-5-cyano-4-methylthio-1*H*-pyrimidine-6-thione (**19**) with bromoketone **2** in the presence of EtONa in EtOH afforded thieno[2,3-*d*]pyrimidine **20** (Scheme 3).

Using thieno[2,3-*b*]pyridine **18a** as an example, we examined the possibility of removing the protective groups present in the molecule with the aim of preparing free α-amino acid. We found that the carbomethoxy group was readily hydrolyzed in an aqueous-alcoholic mixture at room temperature to give the corresponding acid **21** (Scheme 4). The methoxy group is labile to an extent that hydrolysis partially proceeded under the conditions of the Thorpe—Ziegler reaction, the trifluoroacetyl group remaining intact. Under more drastic conditions (50 °C), the trifluoroacetyl group was also hydrolyzed to form the corresponding α-amino acid **22**.

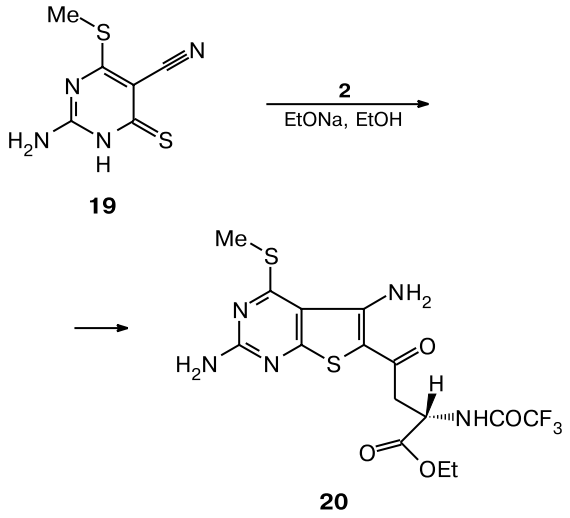
Hydrolysis giving rise to α-amino acid can also be performed under acidic conditions. Storage of compound **18a** in a 30% aqueous solution of hydrochloric acid at 20 °C for 24 h afforded amino acid **22**. Refluxing of compound **18a** in the same medium for 2 h gave rise to a product identified as 4,6-dimethylthieno[2,3-*b*]pyridine-3(2*H*)-one hydrochloride[7,8] (**23**) (see Scheme 4).

The structures of the compounds synthesized in the present study were confirmed by physical and chemi-

Scheme 2



Scheme 3



16	R^1	R^2	R^3	16	R^1	R^2	R^3
a	Me	H	Me	**i**	H	CN	NH_2
b	H	H	2-thienyl	**j**	CF_3	H	Me
c	H	H	4-pyridyl	**k**	CF_3	H	Ph
d	H		$(CH_2)_3$	**l**	*p*-$MeOC_6H_4$	H	Ph
e	H	H	Me	**m**	Ph	H	2-thienyl
f	H	Ac	Me	**n**	*p*-ClC_6H_4	H	2-thienyl
g	H		$(CH_2)_4$	**o**	*p*-FC_6H_4	H	Ph
h	H	H	*m*-$MeOC_6H_4$	**p**	Et	H	Me

Note. For the substituents R^1, R^2, and R^3 in compounds **17** and **18**, see Tables 1 and 2.

cal methods (Tables 1 and 2; see the Experimental section).

We believe that the configuration of the chiral fragment in the reaction products remained unchanged in the course of the synthesis and it corresponds to that in the starting compound **2**. The fact that a series of the compounds synthesized possess optical activity is evidence in favor of this assumption. However, this assumption cannot be confirmed for thieno[2,3-*b*]pyridines **18a—n** because their solutions are colored and substantially absorb

Scheme 4

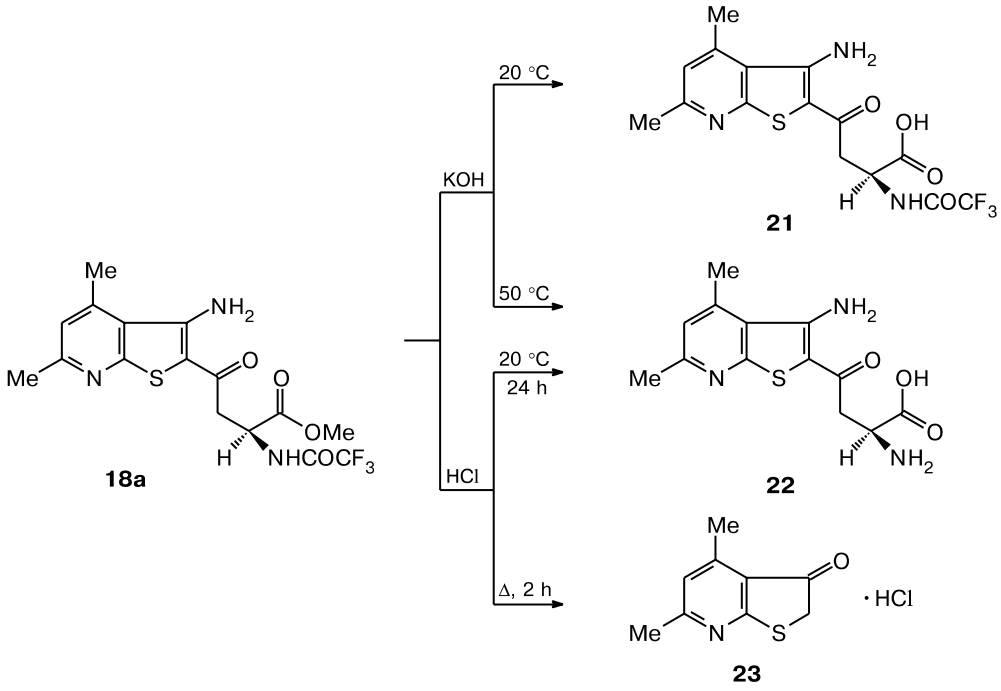


Table 1. Physicochemical and spectroscopic characteristics of compounds **17a—f**

Compound	R^1	R^2	R^3	Yield (%)	M.p. /°C	$[\alpha]_D^{20}$, DMSO (concentration /g (100 mL)$^{-1}$)	IR, ν/cm^{-1}	^{1}H NMR (DMSO-d_6), δ (J/Hz)
17a	Me	H	Me	72	138	−17.0 (1.0)	3276 (NH); 2228 (CN); 1748, 1732, 1710, 1580 (CO)	2.52*, 2.72 (both s, 3 H each, Me); 3.28** (m, 2 H, CH_2); 3.61 (s, 3 H, OMe); 4.22 (s, 2 H, SCH_2); 4.72 (m, 1 H, CH); 7.78 (s, 1 H, $CH_{pyridyl}$); 8.63 (br.m, 1 H, NH)
17b	*p*-$MeOC_6H_4$	H	Ph	83	174	−20.9 (6.5)	3304 (NH); 2220 (CN); 1744, 1720, 1700, 1612 (CO)	3.30** (m, 2 H, CH_2); 3.63 (s, 3 H, Me); 3.89 (s, 3 H, OMe); 4.41 (s, 2 H, SCH_2); 4.77 (m, 1 H, CH); 7.12 (d, 2 H, CH_{arom}, J = 9.9); 7.48 (m, 3 H, CH_{arom}); 7.81 (d, 2 H, CH_{arom}, J = 9.9); 7.93 (s, 1 H, $CH_{pyridyl}$); 8.21 (m, 2 H, CH_{arom}); 9.79 (br.m, 1 H, NH)
17c	*p*-FC_6H_4	H	Ph	87	159	−19.0 (9.0)	3300 (NH); 2220 (CN); 1736, 1724, 1700, 1608 (CO)	3.51** (m, 2 H, CH_2); 3.60 (s, 3 H, OMe); 4.39 (s, 2 H, SCH_2); 4.62 (m, 1 H, CH); 7.45 (d.d, 2 H, CH_{arom}, J = 8.1); 7.64 (m, 3 H, CH_{arom}); 7.93 (m, 3 H, CH_{arom}); 8.32 (s, 2 H, CH_{arom}); 9.21 (br.m, 1 H, NH)
17d	H	H	Me	69	135	−15.1 (4.5)	3272 (NH); 2228 (CN); 1748, 1732, 1704, 1564 (CO)	2.55* (s, 3 H, Me); 3.41** (m, 2 H, CH_2); 3.72 (s, 3 H, OMe); 4.19 (s, 2 H, SCH_2); 4.75 (m, 1 H, CH); 7.22, 8.05 (both s, 1 H each, $CH_{pyridyl}$); 8.64 (br.m, 1 H, NH)
17e	H	Ac	Me	76	164	−17.9 (7.8)	3288 (NH); 2228 (CN); 1756, 1720, 1712, 1580 (CO)	2.52* (s, 3 H, Me); 2.63 (s, 3 H, Ac); 3.32** (m, 2 H, CH_2); 3.71 (s, 3 H, OMe); 4.29 (s, 2 H, SCH_2); 4.68 (m, 1 H, CH); 8.17 (s, 1 H, $CH_{pyridyl}$); 9.74 (br.m, 1 H, NH)
17f	Et	H	Me	70	136	−18.0 (4.0)	3288 (NH); 2228 (CN); 1748, 1732, 1712, 1564 (CO)	1.25 (t, 3 H, $C\underline{H}_3CH_2$, J = 7.5); 2.31 (s, 3 H, Me); 2.71 (q, 2 H, $CH_3C\underline{H}_2$, J = 7.5); 3.42** (m, 2 H, CH_2); 3.60 (s, 3 H, OMe); 4.25 (s, 2 H, SCH_2); 4.43 (m, 1 H, CH); 7.85 (s, 1 H, $CH_{pyridyl}$); 8.59 (br.s, 1 H, NH)

* The signal is partially overlapped with the signal of the solvent.
** The signal is partially overlapped with the signal of water.

Table 2. Physicochemical and spectroscopic characteristics of compounds **18a—n**

Compound	R^1	R^2	R^3	Yield (%)	M.p. /°C	IR, ν/cm^{-1}	^{1}H NMR (DMSO-d_6), δ (J/Hz)
18a	Me	H	Me	87	87	3488, 3316 (NH, NH_2); 1740, 1712, 1600, 1552 (CO)	2.52*, 2.72 (both s, 3 H each, Me); 3.31** (m, 2 H, CH_2); 3.70 (s, 3 H, OMe); 4.69 (m, 1 H, CH); 7.12 (s, 1 H, $CH_{pyridyl}$); 7.61 (br.s, 2 H, NH_2); 9.88 (br.m, 1 H, NH)
18b	H	H	2-thienyl	92	249	3464, 3316, 3284 (NH, NH_2); 1752, 1796, 1608, 1508 (CO)	3.36** (m, 2 H, CH_2); 3.73 (s, 3 H, OMe); 5.15 (m, 1 H, CH); 7.31 (dd, 1 H, $CH_{thiophene}$, J_1 = 3.5, J_2 = 4.9); 7.70 (d, 1 H, $CH_{thiophene}$, J = 3.5); 7.82 (br.s, 2 H, NH_2); 7.94 (d, 1 H, $CH_{thiophene}$, J = 4.9); 8.01 (d, 1 H, $CH_{pyridyl}$, J = 8.1); 8.49 (d, 1 H, $CH_{pyridyl}$, J = 8.1); 8.92 (br.m, 1 H, NH)

(*to be continued*)

Table 2 (*continued*)

Compound	R^1	R^2	R^3	Yield (%)	M.p. /°C	IR, ν/cm^{-1}	^{1}H NMR (DMSO-d_6), δ (*J*/Hz)
18c	H	H	4-pyridyl	85	215	3420, 3304 (NH, NH_2); 1748, 1724, 1684, 1628 (CO)	3.33** (m, 2 H, CH_2); 3.70 (s, 3 H, OMe); 4.98 (m, 1 H, CH); 8.13 (m, 4 H, 2 $CH_{pyridyl}$ + NH_2); 8.21 (d, 1 H, $CH_{pyridyl}$, *J* = 7.9); 8.74 (m, 3 H, $CH_{pyridyl}$); 9.92 (br.m, 1 H, NH)
18d	H	$(CH_2)_3$		79	101	3490, 3332 (NH, NH_2); 1736, 1718, 1604, 1549 (CO)	2.24 (m, 4 H, —$CH_2C\underline{H}_2CH_2$—); 3.09 (m, 4 H, —$C\underline{H}_2CH_2C\underline{H}_2$—); 3.37** (m, 2 H, CH_2); 3.75 (s, 3 H, OMe); 5.14 (m, 1 H, CH); 7.65 (br.s, 2 H, NH_2); 8.25 (s, 1 H, $CH_{pyridyl}$); 8.75 (br.m, 1 H, NH)
18e	H	H	Me	65	90	3392, 3292 (NH, NH_2); 1744, 1700, 1692, 1628 (CO)	2.71* (s, 3 H, Me); 3.37** (m, 2 H, CH_2); 3.77 (s, 3 H, OMe); 4.78 (m, 1 H, CH); 7.12 (d, 1 H, $CH_{pyridyl}$, *J* = 8.1); 7.64 (br.s, 2 H, NH_2); 8.73 (d, 1 H, $CH_{pyridyl}$, *J* = 8.1); 9.30 (br.m, 1 H, NH)
18f	H	Ac	Me	80	109	3432 (NH); 3324 (NH, NH_2); 1724, 1684, 1616, 1588 (CO)	2.61* (s, 3 H, Me); 2.75 (s, 3 H, Ac); 3.29 (m, 2 H, CH_2); 3.72 (s, 3 H, OMe); 5.01 (m, 1 H, CH); 8.08 (br.s, 2 H, NH_2); 9.11 (s, 1 H, $CH_{pyridyl}$); 9.83 (br.m, 1 H, NH)
18g	H	$(CH_2)_4$		73	98	3489, 3334 (NH, NH_2); 1746, 1725, 1614, 1551 (CO)	1.88 (m, 4 H, —$CH_2C\underline{H}_2C\underline{H}_2CH_2$—); 2.92 (m, 4 H, —$C\underline{H}_2CH_2CH_2C\underline{H}_2$—); 3.33** (m, 2 H, CH_2); 3.75 (s, 3 H, OMe); 5.08 (m, 1 H, CH); 7.73 (br.s, 2 H, NH_2); 8.09 (s, 1 H, $CH_{pyridyl}$); 8.94 (br.m, 1 H, NH)
18h	H	H	*m*-$MeOC_6H_4$	81	187	3470, 3318 (NH, NH_2); 1742, 1790, 1610, 1508 (CO)	3.32** (m, 2 H, CH_2); 3.74, 3.89 (both s, 3 H each, OMe); 4.91 (m, 1 H, CH); 7.12 (d, 1 H, CH_{arom}, *J* = 7.0); 7.43 (t, 1 H, CH_{arom}, *J* = 7.1); 7.65 (m, 2 H, CH_{arom}); 8.02 (m, 3 H, $CH_{pyridyl}$ + NH_2); 8.14 (d, 1 H, $CH_{pyridyl}$); 9.87 (br.m, 1 H, NH)
18i	H	CN	NH_2	65	≥300	2224 (CN); 1724, 1696, 1612, 1592 (CO)	3.29** (m, 2 H, CH_2); 3.73 (s, 3 H, OMe); 4.91 (m, 1 H, CH); 7.57, 7.87 (both br.s, 2 H each, NH_2); 8.83 (s, 1 H, $CH_{pyridyl}$); 9.21 (br.m, 1 H, NH)
18j	CF_3	H	Me	78	79	3496, 3333 (NH, NH_2); 1743, 1722, 1598, 1552 (CO)	2.72 (s, 3 H, Me); 3.33** (m, 2 H, CH_2); 3.75 (s, 3 H, OMe); 4.93 (m, 1 H, CH); 7.35 (br.s, 2 H, NH_2); 7.74 (s, 1 H, $CH_{pyridyl}$); 9.91 (br.m, 1 H, NH)
18k	CF_3	H	Ph	83	163	3528, 3312 (NH, NH_2); 1752, 1724, 1628, 1604 (CO)	3.31** (m, 2 H, CH_2); 3.76 (s, 3 H, OMe); 4.89 (m, 1 H, CH); 7.38 (br.s, 2 H, NH_2); 7.51 (m, 3 H, CH_{arom}); 8.09 (m, 3 H, CH_{arom} + $CH_{pyridyl}$); 9.92 (br.m, 1 H, NH)
18l	*p*-$MeOC_6H_4$	H	Ph	79	188	3480, 3300 (NH, NH_2); 1728, 1700, 1608, 1592 (CO)	3.28** (m, 2 H, CH_2); 3.67, 3.69 (both s, 3 H each, OMe); 4.95 (m, 1 H, CH); 6.81 (br.s, 2 H, NH_2); 7.13 (d, 2 H, CH_{arom}, *J* = 8.5); 7.54 (m, 5 H, CH_{arom}); 7.63 (s, 1 H, $CH_{pyridyl}$); 8.11 (d, 2 H, CH_{arom}, *J* = 3.5); 9.89 (br.m, 1 H, NH)
18m	Ph	H	2-thienyl	85	124	3480, 3322 (NH, NH_2); 1728, 1690, 1590, 1579 (CO)	3.32** (m, 2 H, CH_2); 3.74 (s, 3 H, OMe); 4.91 (m, 1 H, CH); 6.78 (br.s, 2 H, NH_2); 7.05 (dd, 1 H, $CH_{thiophene}$, *J* = 3.5, *J* = 4.9); 7.62—7.75 (m, 7 H, CH_{arom}); 7.91 (d, 1 H, $CH_{thiophene}$, *J* = 3.5); 9.88 (br.m, 1 H, NH)
18n	*p*-ClC_6H_4	H	2-thienyl	90	118	3480, 3316 (NH, NH_2); 1728, 1684, 1600, 1528 (CO)	3.35** (m, 2 H, CH_2); 3.76 (s, 3 H, OMe); 4.94 (m, 1 H, CH); 6.81 (br.s, 2 H, NH_2); 7.12 (dd, 1 H, $CH_{thiophene}$, *J* = 3.5, *J* = 4.9); 7.64—7.77 (m, 6 H, CH_{arom}); 8.03 (d, 1 H, $CH_{thiophene}$, *J* = 3.5); 10.02 (br.m, 1 H, NH)

* The signal is partially overlapped with the signal of the solvent.
** The signal is partially overlapped with the signal of water.

electromagnetic radiation in the spectral region used in a polarimeter (sodium D line). For the above reason, we also failed to reveal whether or not hydrolysis of ester **18a** giving rise to acids **21** and **22** was accompanied by racemization.

Experimental

The IR spectra were recorded on a Specord M-80 instrument (KBr pellets). The ^{1}H NMR spectra were measured on a Bruker AM-300 spectrometer (300.13 MHz). The optical rotation was measured on a CM-2 circular polarimeter using a 0.5-dm path length cell at λ = 589 nm (sodium D line). The specific rotations and concentrations are expressed in (deg mL) (g dm)$^{-1}$ and g (100 mL)$^{-1}$, respectively. Mercaptonitriles **3**, **16a—p**, and **19** were prepared according to procedures described earlier.[4—6] Bromoketone **2** (m.p. 109—110 °C (from *n*-heptane), $[\alpha]_D^{20}$ = +3.2 (*c* 2.26, AcOEt)) was synthesized according to a known procedure[3] from L-aspartic acid.

Methyl (2*S*)-5-{(3*S*)-[4-amino-3-cyano-5-(3-methoxycarbonyl-3-trifluoroacetylaminopropanoyl)-2-thienyl]thio}-4-oxo-2-trifluoroacetylaminopentanoate (4). Ester **2** (0.7 g, 2.2 mmol) was added with stirring to a solution of disodium salt of 1,1-dicyano-2,2-dimercaptoethylene (**3**) (0.166 g, 1 mmol) in 70% aqueous MeOH (5 mL) at 20 °C. The reaction mixture was stirred at 20 °C for 15 min and then water (2 mL) was added. The precipitate that formed was filtered off and recrystallized from MeOH. The yield was 0.55 g (90%), m.p. 186 °C, $[\alpha]_D^{20}$ = +29.0 (*c* 2.8, acetone). Found (%): C, 38.69; H, 2.97; N, 8.93. $C_{20}H_{18}F_6N_4O_8S_2$. Calculated (%): C, 38.71; H, 2.92; N, 9.03. ^{1}H NMR (DMSO-d_6), δ: 3.25 (m, 4 H, CH_2); 3.67 (s, 6 H, OMe); 4.42 (s, 2 H, SCH_2); 5.72 (m, 1 H, CH); 5.87 (m, 1 H, CH); 7.39 (br.s, 2 H, NH_2); 9.65 (br.s, 2 H, NH). IR, ν/cm^{-1}: 3440, 3328, 3300 (NH, NH_2); 2228 (CN); 1744, 1728, 1708, 1621 (CO).

3,4-Diamino-2,5-bis[(3*S*)-3-methoxycarbonyl-3-trifluoroacetylaminopropanoyl]thieno[2,3-*b*]thiophene (5). A solution of ester **4** (0.42 g, 0.7 mmol) and Et_3N (0.01 mL, 0.72 mmol) in MeOH (5 mL) was refluxed for 2 h. Then the reaction mixture was cooled, the solvent was evaporated under reduced pressure, and the residue was recrystallized from MeOH. The yield was 0.36 g (86%), m.p. 224 °C, $[\alpha]_D^{20}$ = +58.6 (*c* 2.8, acetone). Found (%): C, 38.73; H, 2.95; N, 8.89. $C_{20}H_{18}F_6N_4O_8S_2$. Calculated (%): C, 38.71; H, 2.92; N, 9.03. ^{1}H NMR (DMSO-d_6), δ: 3.25 (m, 4 H, CH_2); 3.67 (s, 6 H, OMe); 4.95 (m, 2 H, 2 CH); 8.15 (br.s, 4 H, NH_2); 9.92 (br.s, 2 H, NH). IR, ν/cm^{-1}: 3468, 3352, 3316 (NH, NH_2); 1724, 1712 (CO).

Methyl (2*S*)-4-(3-amino-4-cyano-5-methylthio-2-thienyl)-4-oxo-2-trifluoroacetylaminobutanoate (6). Iodomethane (0.32 g, 2.2 mmol) was added with stirring to a solution of salt **3** (0.37 g, 2 mmol) in 70% aqueous MeOH (10 mL) at 20 °C. The reaction mixture was stirred at 20 °C for 15 min and then ester **2** (0.7 g, 2.2 mmol) was added. The reaction mixture was stirred at 20 °C for 30 min and then water (2 mL) was added. The precipitate that formed was filtered off and recrystallized. The yield was 0.71 g (90%), m.p. 66 °C (MeOH), $[\alpha]_D^{20}$ = +44.0 (*c* 5.0, MeOH). Found (%): C, 38.48; H, 3.06; N, 10.81. $C_{13}H_{12}F_3N_3O_4S_2$. Calculated (%): C, 38.49; H, 3.06; N, 10.63. ^{1}H NMR (DMSO-d_6), δ: 2.77 (s, 3 H, SMe); 3.23 (m, 2 H, CH_2); 3.67 (s, 3 H, OMe); 4.90 (m, 1 H, CH); 7.59 (br.s, 2 H, NH_2); 9.92 (br.s, 1 H, NH). IR, ν/cm^{-1}: 3460, 3339, 3308 (NH, NH_2); 2225 (CN); 1714, 1702 (CO).

Methyl (2*S*)-4-(3-amino-5-anilino-4-cyano-2-thienyl)-4-oxo-2-trifluoroacetylaminobutanoate (9). A 10% aqueous KOH solution (1.4 mL) and phenyl isothiocyanate (**7**) (0.270 g, 2 mmol) were added to a solution of malonodinitrile (**8**) (0.14 g, 2.1 mmol) in MeOH (5 mL) at 20 °C. The reaction mixture was stirred at 20 °C for 15 min and then ester **2** (0.7 g, 2.2 mmol) was added. The reaction mixture was stirred at 20 °C for 20 min, after which water (2 mL) was added. The precipitate that formed was filtered off and recrystallized from MeOH. The yield was 0.6 g (69%), m.p. 194 °C, $[\alpha]_D^{20}$ = +45.0 (*c* 4.0, MeOH). Found (%): C, 49.11; H, 3.46; N, 12.61. $C_{18}H_{15}F_3N_4O_4S$. Calculated (%): C, 49.09; H, 3.43; N, 12.72. ^{1}H NMR (DMSO-d_6), δ: 2.93 (m, 2 H, CH_2); 3.63 (s, 3 H, OMe); 4.85 (m, 1 H, CH); 7.20—7.50 (m, 5 H, Ph); 7.67 (br.s, 2 H, NH_2); 9.78 (m, 1 H, NH); 10.50 (br.s, 1 H, NHPh). IR, ν/cm^{-1}: 3464, 3312, 3292 (NH, NH_2); 2228 (CN); 2200, 1724, 1684 (CO).

Methyl (2*S*)-4-(4-amino-2-anilinothiazol-5-yl)-4-oxo-2-trifluoroacetylaminobutanoate (12). A 10% aqueous KOH solution (1.4 mL) and phenyl isothiocyanate (**7**) (0.270 g, 2 mmol) were added to a solution of cyanamide (**11**) (0.09 g, 2.2 mmol) in MeOH (5 mL) at 20 °C. The reaction mixture was stirred at 20 °C for 5 min and then ester **2** (0.7 g, 2.2 mmol) was added. The reaction mixture was stirred at 20 °C for 20 min, after which water (2 mL) was added. The precipitate that formed was filtered off and recrystallized from MeOH. The yield was 0.42 g (55%), m.p. 171 °C, $[\alpha]_D^{20}$ = +52.3 (*c* 4.2, acetone). Found (%): C, 46.11; H, 3.71; N, 13.55. $C_{16}H_{15}F_3N_4O_4S$. Calculated (%): C, 46.15; H, 3.63; N, 13.46. ^{1}H NMR (DMSO-d_6), δ: 2.93 (m, 2 H, CH_2); 3.66 (s, 3 H, OMe); 4.87 (m, 1 H, CH); 7.12—7.75 (m, 5 H, Ph); 7.95 (br.s, 2 H, NH_2); 9.85 (br.s, 1 H, NH); 10.85 (br.s, 1 H, NHPh). IR, ν/cm^{-1}: 3444, 3324, 3276 (NH, NH_2); 2960 (NH); 1736, 1696 (CO).

Methyl (2*S*)-3-(2-dicyanomethylene-2,3-dihydrothiazol-4-yl)-2-trifluoroacetylaminopropanoate (15). Methanol (5 mL) was added to a solution of KSCN (0.21 g, 2 mmol) in water (2 mL). Then ester **2** (0.7 g, 2.2 mmol) was added with stirring at 20 °C. After precipitation of rhodanide, malonodinitrile (**8**) (0.14 g, 2.1 mmol) and a 10% aqueous KOH solution (0.4 mL) were added (the precipitate was dissolved). The reaction mixture was stirred at 40 °C for 1 h, cooled, and diluted to twice its volume with water. The precipitate that formed was filtered off and recrystallized from 50% aqueous MeOH. The yield was 0.3 g (46%), m.p. 228 °C, $[\alpha]_D^{20}$ = –95.0 (*c* 1.5, acetone). Found (%): C, 41.59; H, 2.68; N, 16.55. $C_{12}H_9F_3N_4O_3S$. Calculated (%): C, 41.62; H, 2.62; N, 16.18. ^{1}H NMR (DMSO-d_6), δ: 3.10 (m, 2 H, CH_2); 3.70 (s, 3 H, OMe); 4.77 (m, 1 H, CH); 6.77 (s, 1 H, $CH_{thiazole}$); 9.93 (m, 1 H, NH); 13.21 (br.s, 1 H, NH). IR, ν/cm^{-1}: 3344, 3108 (NH); 2212, 2188 (CN); 1756, 1708 (CO).

(*S*)-*N*-Trifluoroacetyl-5-(3-cyano-2-pyridylthio)-4-oxonorvaline methyl esters 17a—f (general procedure). A 10% aqueous KOH solution (0.56 mL) was added to a solution of pyridinethione **16** (1 mmol) in DMF (1.5 mL) at 20 °C. The reaction mixture was stirred for 10 min (if necessary, the reaction mixture was heated to 40—50 °C to increase solubility). The resulting solution was filtered through a folded filter. Ester **2** (1.1 mmol) was added with stirring to the filtrate at 20 °C. The reaction mixture was stirred at 20 °C for 5 min. Then water (2 mL) was added. The precipitate that formed was filtered off,

successively washed with water, ethanol, and hexane, dried, and recrystallized from MeOH.

Methyl (2*S*)-4-(3-aminothieno[2,3-*b*]pyridin-2-yl)-4-oxo-2-trifluoroacetylaminobutanoates 18a—n (general procedure). ***A.*** Methyl ester **17** (1 mmol) was dispersed in dry MeOH (5 mL) and a 5% MeONa solution in MeOH (1 mL) was added at 20 °C. The reaction mixture was refluxed for 15 min and then cooled, after which water (3 mL) was added. The precipitate that formed was filtered off and recrystallized from MeOH.

B. Pyridinethione **16** (1 mmol) and ester **2** (1.1 mmol) were refluxed in MeOH (10 mL) containing MeONa (1.3 mmol) for 20 min. After cooling, the reaction mixture was diluted to twice its volume with water. The precipitate that formed was filtered off and recrystallized from MeOH.

Ethyl (2*S*)-4-(2,5-diamino-4-methylthiothieno[2,3-*d*]pyrimidin-6-yl)-4-oxo-2-trifluoroacetylaminobutanoate (20). 2-Amino-5-cyano-4-methylthio-1*H*-pyrimidine-6-thione (**19**) (0.396 g, 2 mmol) was dispersed in anhydrous EtOH (10 mL). Then EtONa (0.1 g) and ester **2** (0.7 g, 2.2 mmol) were added with stirring at 20 °C. The reaction mixture was stirred for 10 min, refluxed for 30 min, cooled, and diluted to twice its volume with water. The precipitate that formed was filtered off and recrystallized from EtOH. The yield was 0.8 g (88%), m.p. 216 °C. Found (%): C, 39.69; H, 4.05; N, 15.62. $C_{15}H_{18}F_3N_5O_4S_2$. Calculated (%): C, 39.73; H, 4.00; N, 15.44. ^{1}H NMR (DMSO-d_6), δ: 1.93 (t, 3 H, $\underline{Me}CH_2O$, J = 6.7 Hz); 2.68 (s, 3 H, SMe); 3.36 (m, 2 H, CH_2); 4.14 (q, 2 H, $MeC\underline{H_2}O$, J = 6.7 Hz); 4.86 (m, 1 H, CH); 7.11 and 7.52 (both br.s, 2 H each, NH_2); 9.55 (br.s, 1 H, NH). IR, ν/cm^{-1}: 3456, 3300 (NH, NH_2); 1712, 1616 (CO).

(2*S*)-4-(3-Amino-4,6-dimethylthieno[2,3-*b*]pyridin-2-yl)-4-oxo-2-trifluoroacetylaminobutanoic acid (21). Ester **18a** (0.4 g, 1 mmol) was added with stirring to a 5% aqueous KOH solution (10 mL). The suspension was stirred at 20 °C for 4 h and then filtered through a folded filter. The filtrate was acidified with 10% HCl to pH 5. The precipitate that formed was filtered off, successively washed with water, EtOH, and hexane, and dried to obtain an analytically pure sample. The yield was 0.3 g (77%), m.p. 165 °C. Found (%): C, 45.99; H, 4.15; N, 10.52. $C_{15}H_{16}F_3N_3O_4S$. Calculated (%): C, 46.03; H, 4.12; N, 10.74. ^{1}H NMR (DMSO-d_6), δ: 2.49 and 2.72 (both s, 3 H each, Me); 3.25 (m, 2 H, CH_2); 4.87 (m, 1 H, CH); 7.05 (s, 1 H, CH_{Het}); 7.65 (br.s, 2 H, NH_2); 9.75 (br.m, 1 H, NH). IR, ν/cm^{-1}: 3400, 3316, 3275 (NH, NH_2); 1712, 1652 (CO).

(2*S*)-2-Amino-4-(3-amino-4,6-dimethylthieno[2,3-*b*]pyridin-2-yl)-4-oxobutanoic acid (22). ***A.*** Methyl ester **18a** (0.4 g, 1 mmol) was added with stirring to a 5% aqueous KOH solution (10 mL). The suspension was stirred at 20 °C for 4 h and then at 50 °C for 1 h, after which the reaction mixture was acidified to pH 6 by adding 10% HCl. The precipitate that formed was filtered off, washed with water, and recrystallized from MeOH. The yield was 0.15 g (51%), m.p. 260 °C.

B. Compound **18a** (0.4 g, 1 mmol) was dissolved in 30% HCl (15 mL). The reaction mixture was kept at 20 °C for 24 h, filtered through a folded filtered, and acidified to pH 6 by adding a 10% KOH solution.The precipitate that formed was filtered off, washed with water, and recrystallized. The yield was 0.17 g (58%), m.p. 260 °C (MeOH). Found (%): C, 52.78; H, 56.65; N, 14.52. $C_{13}H_{17}N_3O_3S$. Calculated (%): C, 52.86; H, 5,80; N, 14.23. ^{1}H NMR (CF_3COOD), δ: 2.61 and 2.75 (both s, 3 H each, Me); 3.45 (m, 2 H, CH_2); 4.95 (m, 1 H, CH); 7.25 (s, 1 H, CH_{Het}); 7.40 (br.s, 1 H, NH). IR, ν/cm^{-1}: 3388, 3284 (NH, NH_2); 1596, 1548 (CO).

2,6-Dimethylthieno[2,3-*b*]pyridin-3(2*H*)-one hydrochloride (23). Methyl ester **18a** (0.8 g, 2 mmol) was dissolved in 30% HCl (15 mL) and refluxed for 2 h. After cooling, the precipitate that formed was filtered off and washed with a small amount of water. The yield was 0.3 g (70%), t.subl. 237 °C.[7,8]

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