Reactions of *N*-(2-chloroacetyl)-α-amino acids with 3-cyanopyridine-2(1*H*)-thiones. New promising route to 3,4-dihydropyrido[3′,2′:4,5]thieno[3,2-*e*][1,4]diazepine-2(1*H*),5-diones

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The reactions of *N*-(2-chloroacetyl)-α-amino acids with 3-cyanopyridine-2(1*H*)-thiones afforded *N*-(3-aminothieno[2,3-*b*]pyridin-2-ylcarbonyl)-α-amino acids. Heating of the latter smoothly produced 3,4-dihydropyrido[3′,2′:4,5]thieno[3,2-*e*][1,4]diazepine-2(1*H*),5-diones in high yields.

Key words: *N*-(2-chloroacetyl)-α-amino acids, 3-cyanopyridine-2(1*H*)-thiones, *N*-(3-aminothieno[2,3-*b*]pyridin-2-ylcarbonyl)-α-amino acids, 3,4-dihydropyrido[3′,2′:4,5]thieno[3,2-*e*][1,4]diazepine-2(1*H*),5-diones, Thorpe—Ziegler cyclization.

3,4-Dihydrobenzo[1,4]diazepine-2(1*H*),5-diones are known as potential antitumor,[1,2] anesthetic,[3—5] hypotensive,[3—5] and antiamebic[6] drugs, bactericides,[7] neuroleptics,[8] and herbicides.[9] Diazepinones are also used as the starting compounds in the synthesis of biologically active diazepines.[2,5,10—13] 3,4-Dihydro[1,4]diazepine-2(1*H*),5-diones fused with a heterocycle can also be of practical interest. 3,4-Dihydro[1,4]diazepine-2(1*H*),5-diones fused with imidazole,[14—22] indole,[23] pyridine[24], thiophene,[24,25] isothiazole,[26] isoselenoazole,[26] and quinoline[27] are known, whereas 3,4-dihydropyrido[3′,2′:4,5]thieno[3,2-*e*][1,4]diazepine-2(1*H*),5-diones were not described in the literature.

Many procedures were developed for the synthesis of systems containing the 3,4-dihydro[1,4]-diazepine-2(1*H*),5-dione fragment.[2—35]

Among the drawbacks of the available methods is the necessity of introducing the corresponding functional groups at a specified position of the molecule followed by activation of these groups, for example, by transforming into 1,3-oxazine-2,6-dione derivatives. It is apparent that in the case of the starting substrates containing other functional groups, which are labile under reaction conditions, these methods have very limited application due to the possibility of competitive reactions.

We developed a new procedure for the synthesis of 3,4-dihydropyrido[3′,2′:4,5]thieno[3,2-*e*][1,4]diazepine-2(1*H*),5-diones, which differs from the known methods in that a fragment, which is ready to undergo cyclization and does not require additional activation, is generated as a result of successive (domino) reactions proceeding regioselectively under rather mild conditions in high yield, and cyclization occurs upon heating of *N*-(thieno[2,3-*b*]pyridin-2-ylcarbonyl)-α-amino acid without a solvent (it should be noted that analogous thermal cyclization has earlier been carried out for *N*-(2-aminobenzoyl)glycine[35]). We developed the new method based on the studies of the reactions of 3-cyanopyridine-2(1*H*)-thiones with chloroacetic acid amides.[36,37]

In the present study, we examined the reactions of *N*-(2-chloroacetyl)-α-amino acids **1a—e** with 3-cyanopyridine-2(1*H*)-thiones **2a—g**.

We used pyridinethiones **2a—g** as the starting reagents. The methods for the synthesis of these compound were well-developed.[36—40] *N*-Chloroacetyl-α-amino acids were prepared from natural α-amino acids and chloroacetyl chloride according to standard procedures (see the Experimental section).

The reactions of mercaptonitriles with electrophiles were studied in sufficient detail.[36—40] Based on the results of these investigations, we assumed that the reactions of *N*-chloroacetyl-α-amino acids **1a—e** with 3-cyanopyridine-2(1*H*)-thiones **2a—g** proceed according to Scheme 1.

The first step of the reaction involves the nucleophilic displacement of the chlorine atom by the thiolate anion to form *N*-[(3-cyanopyridin-2-ylthio)acetyl]-α-amino acids **3**, which is confirmed by isolation of some of these compounds in pure form. These reactions with the use of amides of natural optically active amino acids afford optically active products **3**. The properties and results of analysis of acylated amino acids **3a—f** are given in Table 1.

The second step involves Thorpe—Ziegler cyclization under the action of a base to produce *N*-(thieno[2,3-*b*]pyridin-2-ylcarbonyl)-α-amino acids **4**. We studied the reactions of compounds **2a—g** with *N*-chloro-

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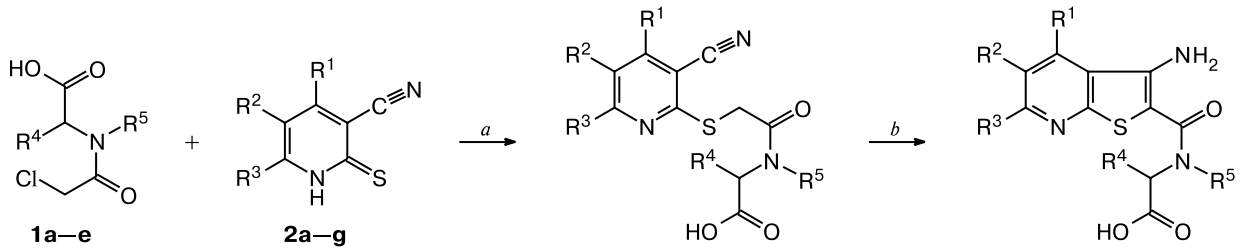
Scheme 1



1		R^4	R^5
a	(Gly)	H	H
b	(L-Ala)	Me	H
c	(L-Val)	Pr^i	H
d	(L-Phe)	Bn	H
e	(L-Pro)	$-(CH_2)_3-$	

2	R^1	R^2	R^3
a	Me	H	Me
b	H	H	4-pyridyl
c	H	Ac	Me
d	H	CN	NH_2
e	CF_3	H	Ph
f	Ph	H	2-thienyl
g	Me	H	CF_3

3	R^1	R^2	R^3	R^4	R^5
a	Me	H	Me	H	H
b	Me	H	Me	Me	H
c	Me	H	Me	Bn	H
d	Me	H	Me	$-(CH_2)_3-$	
e	Me	H	CF_3	H	H
f	Ph	H	2-thienyl	H	H

4	R^1	R^2	R^3	R^4	R^5
a	Me	H	Me	H	H
b	H	H	4-pyridyl	H	H
c	H	Ac	Me	H	H
d	H	CN	NH_2	H	H
e	CF_3	H	Ph	H	H
f	Ph	H	2-thienyl	H	H
g	Me	H	CF_3	H	H
h	Me	H	Me	Me	H
i	Me	H	Me	Pr^i	H
j	Me	H	Me	Bn	H
k	Me	H	Me	$-(CH_2)_3-$	

a. KOH; *b*. 1) KOH, 2) HCl.

acetylglycine (**1a**). It was found that pyridinethiones containing Ar and Het substituents at positions 4 and 6 are much more difficult to subject to Thorpe—Ziegler cyclization, and a much longer reaction time and higher temperature are required for completion of the reaction compared to the reactions with alkyl-substitueted pyridinethiones. This fact should be taken into account when planning the synthesis because the use of more drastic reaction conditions increases the probability of decomposition of both the starting *N*-chloroacetyl derivative of amino acid and intermediate **3**. We also carried out the reactions of 3-cyano-4,6-dimethylpyridine-2(1*H*)-thione (**2a**) with *N*-chloroacyl derivatives of optically active amino acids, such as L-alanine, L-phenylalanine, L-valine, and L-proline. However, we failed to evaluate the optical activity of the resulting compounds **4a—k** due to strong absorption by solutions of 3-aminothieno[2,3-*b*]pyridines in the spectral region used in a polarimeter (sodium D line). The properties of compounds **4** are given in Table 2.

When studying the properties of *N*-(3-amino-4,6-dimethylthieno[2,3-*b*]pyridin-2-ylcarbonyl)glycine (**4a**),

Table 1. Spectroscopic characteristics of compounds **3a—f**

Compound	IR, ν/cm^{-1}	^{1}H NMR (DMSO-d$_6$, δ, *J*/Hz)
3a	3304 (NH), 2216 (CN), 1716 (COOH), 1628, 1584 (CO)	2.52, 2.75 (both s, 3 H each, Me); 3.75 (d, 2 H, CH_2 *J* = 3.7); 4.05 (s, 2 H, SCH_2); 7.10 (s, 1 H, CH of pyridine); 8.41 (br.m, 1 H, NH)
3b	3304 (NH), 2216 (CN), 1720 (COOH), 1624, 1584 (CO)	1.27 (d, 3 H, Me, *J* = 7.3); 2.35, 2.45 (both s, 3 H each, Me); 4.02 (s, 2 H, SCH_2); 4.25 (dq, 1 H, CH, *J* = 7.3, *J* = 7.5); 7.12 (s, 1 H, CH of pyridine); 8.43 (d, 1 H, NH, *J* = 7.5)
3c	3280 (NH), 2220 (CN), 1736 (COOH), 1624, 1548 (CO)	2.30, 2.40 (both s, 3 H each, Me); 3.02 (m, 2 H, CH_2); 3.89 (s, 2 H, SCH_2); 4.25 (m, 1 H, CH); 7.05 (s, 1 H, CH of pyridine); 7.15 (m, 5 H, Ar); 8.25 (br.m, 1 H, NH)
3d	2224 (CN), 1728 (COOH), 1620 (CO)	1.90 (m, 2 H, CH_2); 2.21 (m, 1 H, CH_2); 2.35, 2.45 (both s, 3 H each, Me); 3.41 (m, 1 H, CH_2); 3.75 (m, 2 H CH_2); 4.15 (s, 2 H, SCH_2); 4.22 (m, 1 H, CH); 7.14 (s, 1 H, CH of pyridine)
3e	3312 (NH), 2228 (CN), 1736 (COOH), 1636, 1556 (CO)	2.61 (s, 3 H, Me); 3.70 (br.s, 2 H, CH_2); 4.10 (s, 2 H, SCH_2); 7.63 (s, 1 H, CH of pyridine); 8.28 (br.s, 1 H, NH)
3f	3292 (NH), 2212 (CN), 1720 (COOH), 1640, 1564 (CO)	3.75 (d, 2 H, CH_2, *J* = 4.8); 4.15 (s, 2 H, SCH_2); 7.23 (t, 1 H, CH of thiophene, *J* = 3.5); 7.55 (m, 3 H, Ar); 7.70 (m, 3 H, CH_{Ar} + CH of pyridine); 8.09 (br.m, 1 H, NH); 8.62 (m, CH of thiophene)

Note. *c*/g·100 cm^{-3}: 8.5 (**3b**), 2.8 (**3c**), 5.03 (**3d**); $[\alpha]_D^{20}$ (K salt in water): −47.2 (**3b**), −36 (**3c**), −36.1 (**3d**).

Table 2. Spectroscopic characteristics of compounds **4a—k**

Compound	IR, ν/cm^{-1}	^{1}H NMR (DMSO-d$_6$, δ, *J*/Hz)
4a	3380, 3320 (NH_2, NH), 1700 (COOH), 1604, 1548 (CO)	2.52, 2.72 (both s, 3 H each, Me); 3.70 (d, 2 H, CH_2, J = 5.9); 7.10 (s, 1 H, CH of pyridine); 7.91 (t, 1 H, NH, J = 5.9)
4b	3336, 3316 (NH_2, NH), 1700 (COOH), 1604, 1524 (CO)	3.79 (d, 2 H, CH_2, J = 5.5); 7.25 (br.s, 2 H, NH_2); 8.02 (t, 1 H, NH, J = 5.5); 8.13 (d, 2 H, CH of pyridine, J = 3.9); 8.20 (d, 1 H, CH of pyridine, J = 8.5); 8.63 (d, 1 H, CH of pyridine, J = 8.5); 8.75 (d, 2 H, CH of pyridine, J = 3.9)
4c	3448, 3324 (NH, NH_2), 1696 (COOH), 1676, 1616, 1588 (CO)	2.62 (s, 3 H, Me); 2.75 (s, 3 H, Ac); 3.80 (d, 2 H, CH_2, J = 6.1); 7.32 (br.s, 2 H, NH_2); 8.05 (t, 1 H, NH, J = 6.1); 9.13 (s, 1 H, CH of pyridine)
4d	3428, 3320, 3216 (NH, NH_2), 2224 (CN), 1700 (COOH), 1640, 1520, (CO)	3.75 (d, 2 H, CH_2, J = 4.9); 7.12, 7.30 (both br.s, 2 H each, NH_2); 7.71 (t, 1 H, NH, J = 4.9); 8.52 (s, 1 H, CH of pyridine)
4e	3516, 3324 (NH, NH_2), 1720 (COOH), 1604, 1540 (CO)	3.85 (d, 2 H, CH_2, J = 4.9); 6.75 (br.s, 2 H, NH_2); 7.55 (m, 3 H, CH_{Ar} + + CH of pyridine); 8.25 (m, 3 H, Ar); 8.35 (t, 1 H, NH, J = 4.9)
4f	3488, 3388, 3448 (NH, NH_2), 1732 (COOH), 1608, 1536 (CO)	3.81 (d, 2 H, CH_2, J = 5.5); 5.80 (br.s, 2 H, NH_2); 7.15 (dd, 1 H, CH of thiophene, J = 3.6, J = 4.9); 7.64 (m, 5 H, Ar); 7.72 (m, 2 H, CH of pyridine + CH of thiophene); 8.03 (d, 1 H, CH of thiophene, J = 3.6); 8.10 (t, 1 H, NH, J = 5.5)
4g	3452, 3331 (NH, NH_2), 1743 (COOH), 1491, 1579 (CO)	2.93 (s, 3 H, Me); 3.91 (d, 2 H, CH_2, J = 5.5); 6.94 (br.s, 2 H, NH_2); 7.65 (s, 1 H, CH of pyridine); 8.25 (t, 1 H, NH, J = 5.5)
4h	3448,3388, 3324 (NH, NH_2), 1700 (COOH), 1604, 1552 (CO)	1.35 (d, 3 H, Me, J = 7.3); 2.45, 2.70 (both s, 3 H each, Me); 4.35 (dq, 1 H, CH, J = 6.7, J = 7.3); 6.82 (br.s, 2 H, NH_2); 7.12 (s, 1 H, CH of pyridine); 7.92 (d, 1 H, NH, J = 6.7, J = 7.3)
4i	3472, 3396, 3336 (NH, NH_2), 1704 (COOH), 1604, 1556 (CO)	0.95 (t, 6 H, CH$\underline{Me}_2$, J = 7.3); 2.15 (m, 1 H, C$\underline{H}Me_2$); 2.45, 2.70 (both s, 3 H each, Me); 4.35 (m, 1 H, CH); 6.75 (br.s, 2 H, NH_2); 7.03 (s, 1 H, CH of pyridine); 7.35 (d, 1 H, NH, J = 6.7)
4j	3484, 3324 (NH, NH_2), 1724 (COOH), 1612, 1552 (CO)	2.45, 2.70 (both s, 3 H each, Me); 3.15 (m, 2 H, CH_2); 4.61 (dt, 1 H, CH, J = 7.3, J = 6.1); 7.03 (s, 1 H, CH of pyridine); 7.25 (m, 5 H, Ar); 7.75 (d, 1 H, NH, J = 6.1)
4k	3344 (NH_2), 1728 (COOH), 1600, 1548 (CO)	2.15 (m, 4 H, CH_2CH_2); 2.45, 2.70 (both s, 3 H each, Me); 3.78 (m, 2 H, CH_2N); 4.51 (m, 1 H, CH); 6.84 (br.s, 2 H, NH_2); 7.05 (s, 1 H, CH of pyridine)

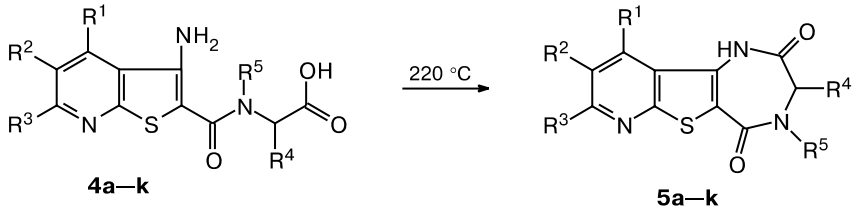
we found that in the course of heating to the melting point, compound **4a** first melted, then solidified, and again melted at higher temperature. Analysis of the resulting product by ^{1}H NMR spectroscopy revealed that the spectrum has a singlet at δ 10.2 characteristic of the amide group (it should be noted that the ^{1}H NMR spectrum of compound **4a** does not show a signal of the amino group due to deuterium exchange). The IR spectrum of the product has a narrow band at 3412 cm^{-1} characteristic of secondary amide instead of a broad absorption band at 3380 cm^{-1} characteristic of the amino group. Besides, the IR spectrum shows two bands at 1690 and 1584 cm^{-1} characteristic of the carbonyl fragment of the CONH group instead of the absorption band of the carboxy group at 1700 cm^{-1}. The mass spectrum has a molecular ion peak at *m/z* 261 (18 units lower than that of the starting compound), which indicates that the reaction was accompanied by elimination of a water molecule. In addition, this spectrum contains ion peaks at *m/z* 232 [M – $NHCH_2$], 205 [M – $NHCH_2CO$], 190, and 176. The substance under consideration is insoluble in 10% aqueous $KHCO_3$ and 5% aqueous HCl, which is, presumably, indicative of the absence of both the carboxy and amino groups. The substance is soluble in a 20% KOH solution, which is evidence for the presence of either the primary or secondary amide group.

Based on the results of the present study, we assumed that the resulting compound is a new polyheterocyclic system, *viz.*, 8,10-dimethyl-3,4-dihydropyrido[3′,2′:4,5]thieno[3,2-*e*][1,4]diazepine-2(1*H*),5-dione (**5a**).

Since this reaction was first found for *N*-(thieno[2,3-*b*]pyridin-2-ylcarbonyl)-α-amino acids, we decided to study the field of its application. All compounds **4** synthesized were subjected to thermal treatment (Scheme 2).

Our investigation demonstrated that virtually all *N*-acyl-α-amino acids **4** were transformed into the corresponding 3,4-dihydropyrido[3′,2′:4,5]thieno[3,2-*e*][1,4]diazepine-2(1*H*),5-diones **5**. It was found that the substituents in the pyridine ring have only a slight effect on the course of the reaction. The reaction rate substantially decreases as the size of the substituent in the amino acid fragment increases in the series of glycine, alanine, valine, phenylalanine, and proline. For this reaction, we empirically found that it is optimum to keep the starting amino acids **4** at 220 °C for 1 h. It should be noted that 4-dihydropyrido[3′,2′:4,5]thieno[3,2-*e*][1,4]diazepine-2(1*H*),5-diones **5h—k** prepared from optically active amino acids also exhibit optical activity.

Scheme 2



4,5	R^1	R^2	R^3	R^4	R^5
a	Me	H	Me	H	H
b	H	H	4-pyridyl	H	H
c	H	Ac	Me	H	H
d	H	CN	NH_2	H	H
e	CF_3	H	Ph	H	H
f	Ph	H	2-thienyl	H	H

4,5	R^1	R^2	R^3	R^4	R^5
g	Me	H	CF_3	H	H
h	Me	H	Me	Me	H
i	Me	H	Me	Pr^i	H
j	Me	H	Me	Bn	H
k	Me	H	Me	$-(CH_2)_3-$	

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) in DMSO-d_6 and $CDCl_3$. The optical rotation was measured on a CM-2 circle polarimeter using a 100-mm path length cell at λ = 589 nm (sodium D line). Pyridinethiones **2a—g** were prepared according to procedures described earlier.[36—40]

***N*-Chloroacetyl-α-amino acids 1a—e (general procedure).** Freshly distilled chloroacetyl chloride (0.1 mol) was added dropwise to a suspension of amino acid (0.2 mol) in dry

Table 3. Spectroscopic characteristics of compounds **5a—k**

Compound	IR, ν/cm^{-1}	^{1}H NMR (DMSO-d_6, δ, J/Hz)
5a	3412, 3320 (NH), 1690, 1584, 1604, 1548 (CO)	2.52, 2.72 (both s, 3 H each, Me); 3.71 (d, 2 H, CH_2, J = 5.5); 7.15 (s, 1 H, CH of pyridine); 7.89 (t, 1 H, NH J = 5.5); 10.20 (s, 1 H, NH)
5b	3184, 3052 (NH), 1676, 1648, 1572, 1552 (CO)	3.85 (d, 2 H, CH_2, J = 4.4); 8.05 (d, 2 H, CH of pyridine, J = 5.2); 8.11 (d, 2 H, CH of pyridine, J = 3.9); 8.33 (d, 1 H, CH of pyridine, J = 8.5); 8.60 (m, 2 H, CH of pyridine + NH); 8.75 (d, 2 H, CH of pyridine, J = 5.2); 11.32 (br.s, 1 H, NH)
5c	3212, 3068 (NH), 1688, 1656, 1592, 11564, 1520 (CO)	2.72 (s, 3 H, Me); 2.81 (s, 3 H, Ac); 3.92 (d, 2 H, CH_2, J = 4.4); 8.58 (t, 1 H, NH, J = 4.4); 9.11 (s, 1 H, CH of pyridine); 11.33 (s, 1 H, NH)
5d	3436, 3312, 3184 (NH, NH_2), 2216 (CN), 1692, 1628, 1596, 1520, 1504 (CO)	3.82 (d, 2 H, CH_2, J = 4.4); 7.40 (br.s, 2 H, NH_2); 8.40 (t, 1 H, NH, J = 4.4); 8.55 (s, 1 H, CH of pyridine); 11.00 (s, 1 H, NH)
5e	3440, 3180 (NH), 1716, 1664, 1592, 1544 (CO)	3.85 (d, 2 H, CH_2, J = 4.9); 7.55 (m, 3 H, Ar); 8.25 (m, 2 H, Ar); 8.32 (s, 1 H, CH of pyridine); 9.10 (t, 1 H, NH, J = 4.9); 9.21 (br.s, 1 H, NH)
5f	3368, 3164 (NH), 1696, 1660, 1576, 1536 (CO)	3.85 (d, 2 H, CH_2, J = 5.5); 7.15 (m, 1 H, CH of thiophene); 7.56 (m, 5 H, Ar); 7.68 (m, 2 H, CH of thiophene); 7.90 (s, 1 H, CH of pyridine); 8.02 (m, 1 H, CH of thiophene); 8.51 (s, 1 H, NH); 8.74 (t, 1 H, NH, J = 5.5)
5g	3404, 3331 (NH) 1796, 1660), 1588, 1528 (CO)	2.92 (s, 3 H, Me); 3.89 (d, 2 H, CH_2, J = 4.1); 7.65 (s, 1 H, CH of pyridine); 8.93 (t, 1 H, NH, J = 4.5); 10.41 (s, 1 H, NH)
5h	3420, 3164 (NH), 1696, 1636, 1584, 1556 (CO)	1.35 (d, 3 H, Me, J = 6.6); 2.72, 3.40 (both s, 3 H each, Me); 4.15 (dq, 1 H, CH, J = 6.6, J = 4.3); 7.10 (s, 1 H, CH of pyridine); 8.62 (d, 1 H, NH, J = 6.6); 10.35 (s, 1 H, NH)
5i	3156, 3040 (NH), 1696, 1644, 1584, 1552 (CO)	0.95 (m, 6 H, CH$\underline{Me}_2$); 2.15 (m, 1 H, C$\underline{H}$Me$_2$); 2.53, 2.70 (both s, 3 H each, Me); 3.48 (m, 1 H, CH); 7.02 (s, 1 H, CH of pyridine); 7.35 (d, 1 H, NH, J = 6.1); 10.25 (br.s, 1 H, NH)
5j	3484, 3324 (NH, NH_2), 1724 (COOH), 1612, 1552 (CO)	2.45, 2.70 (both s, 3 H each, Me); 3.15 (m, 2 H, CH_2); 4.33 (m, 1 H, CH); 7.03 (s, 1 H, CH of pyridine); 7.25 (m, 5 H, Ar); 7.75 (d, 1 H, NH, J = 4.4); 10.31 (br.s, 1 H, NH)
5k	3400 (NH), 1700, 1684, 1632, 1552 (CO)	2.01 (m, 4 H, CH_2CH_2); 2.55, 2.75 (both s, 3 H each, Me); 3.83 (m, 2 H, CH_2N); 4.41 (m, 1 H, CH); 6.79 (br.s, 2 H, NH_2); 7.01 (s, 1 H, CH of pyridine)

Note. c/g·100 cm^{-3}: 2.6 (**5h**), 2.8 (**5i**), 1.7 (**5j**), 2.6 (**5k**); $[\alpha]_D^{20}$ (DMSO): +11.3 (**5h**), +10.7 (**5i**), +18.3 (**5j**), +10.9 (**5k**).

MeCN (200 mL) with cooling to ~20 °C. The resulting suspension was stirred at ~20 °C for 48 h. The precipitate of amino acid hydrochloride was filtered off and the filtrate was concentrated to dryness under reduced pressure. The residue was used in subsequent transformation without purification.

***N*-Chloroacetylglycine (1a).** The yield was 95%, m.p. 96 °C (*cf.* lit. data[41]: 98—100 °C). Found (%): C, 31.59; H, 4.06; N, 9.03. $C_4H_6ClNO_3$. Calculated (%): C, 31.70; H, 3.99; N, 9.24. ^{1}H NMR (DMSO-d_6), δ: 3.75 (d, 2 H, CH_2, J = 3.7 Hz); 4.15 (s, 2 H, $ClCH_2$); 8.50 (br.m, 1 H, NH). IR, ν/cm^{-1}: 3318 (NH), 1722 (COOH), 1631, 1574 (CO).

***N*-Chloroacetyl-L-alanine (1b).** The yield was 90%, m.p. 72 °C (*cf.* lit. data[42]: 93 °C), $[\alpha]_D^{20}$ −10.2 (*c* 11, K salt, H_2O). Found (%): C, 36.19; H, 5.01; N, 9.11. $C_5H_8ClNO_3$. Calculated (%): C, 36.27; H, 4.87; N, 8.46. ^{1}H NMR ($CDCl_3$), δ: 1.53 (d, 3 H, Me, J = 6.6 Hz); 4.10 (s, 2 H, $ClCH_2$); 4.51 (dq, 1 H, CH, J = 6.6 Hz, J = 7.4 Hz); 7.20 (d, 1 H, NH, J = 7.4 Hz); 8.50 (br.s, 1 H, COOH). IR, ν/cm^{-1}: 3328 (NH), 1731 (COOH), 1624, 1566 (CO).

***N*-Chloroacetyl-L-valine (1c).** The yield was 98%, m.p. 112 °C (*cf.* lit. data[42]: 114 °C), $[\alpha]_D^{20}$ −13.9 (*c* 7.9, K salt, H_2O). Found (%): C, 43.39; H, 6.36; N, 6.93. $C_7H_{12}ClNO_3$. Calculated (%): C, 43.42; H, 6.25; N, 7.23. ^{1}H NMR ($CDCl_3$), δ: 0.95 (t, 6 H, CH$\underline{Me}_2$, J = 5.9 Hz); 2.15 (m, 1 H, C$\underline{H}$Me$_2$); 4.10 (s, 2 H, $ClCH_2$); 4.59 (m, 1 H, CHNH); 7.15 (d, 1 H, NH, J = 8.1 Hz); 8.50 (br.s, 1 H, COOH). IR, ν/cm^{-1}: 3344 (NH), 1718 (COOH), 1636, 1582 (CO).

***N*-Chloroacetyl-L-phenylalanine (1d).** The yield was 93%, m.p. 119 °C (*cf.* lit. data[42]: 125 °C), $[\alpha]_D^{20}$ +28.5 (*c* 8.4, K salt, H_2O). Found (%): C, 54.59; H, 6.05; N, 6.35. $C_{11}H_{12}ClNO_3$. Calculated (%): C, 54.67; H, 5.00; N, 5.80. ^{1}H NMR ($CDCl_3$), δ: 3.20 (m, 2 H, CH_2); 4.10 (s, 2 H, $ClCH_2$); 4.85 (m, 1 H, CH); 7.05 (br.m, 1 H, NH); 7.25 (m, 2 H, Ar); 7.35 (m, 3 H, Ar); 8.70 (br.s, 1 H, COOH). IR, ν/cm^{-1}: 3356 (NH), 1722 (COOH), 1676, 1552 (CO).

***N*-Chloroacetyl-L-proline (1e).** The yield was 93%, m.p. 101 °C (*cf.* lit. data[42]: 125 °C), $[\alpha]_D^{20}$ −21.7 (*c* 9.2, K salt, H_2O). Found (%): C, 43.96; H, 5.34; N, 7.75. $C_7H_{10}ClNO_3$. Calculated (%): C, 43.88; H, 5.26; N, 7.31. ^{1}H NMR (acetone-d_6), δ: 1.90, 2.25, and 3.75 (all m, 2 H each, CH_2); 4.25 (s, 2 H, $ClCH_2$); 4.40 (m, 1 H, CH). IR, ν/cm^{-1}: 1712 (COOH), 1668, 1576 (CO).

***N*-[(3-Cyanopyridin-2-ylthio)acetyl]-α-amino acids (3a,f) (general procedure).** A 10% aqueous KOH solution (12 mL) and solid *N*-chloroacetyl-α-amino acid **1** (10 mmol) were added to a solution of pyridinethione **2** (10 mmol) in DMF (10 mL) at 20 °C. The reaction mixture was stirred at ~20 °C for 40 min and acidified with 10% HCl to Congo red. Then water (25 mL) was added. The precipitate that formed was filtered off and purified

Table 4. Melting points, yields, and elemental analysis data for compounds **3—5**

Compound	M.p. /°C	Yield (%)	Found / Calculated (%) C	H	N	Molecular formula
3a	104	87	51.53 51.60	4.80 4.69	14.72 15.04	$C_{12}H_{13}N_3O_3S$
3b	230	83	53.11 53.23	5.27 5.15	15.12 14.32	$C_{13}H_{15}N_3O_3S$
3c	192	81	61.65 61.77	5.25 5.18	10.92 11.37	$C_{19}H_{19}N_3O_3S$
3d	83	69	56.37 56.41	5.49 5.37	12.53 13.16	$C_{15}H_{17}N_3O_3S$
3e	228	73	43.37 43.24	3.08 3.02	11.95 12.61	$C_{12}H_{10}F_3N_3O_3S$
3f	212	79	58.60 58.66	3.74 3.69	10.51 10.20	$C_{20}H_{15}N_3O_3S_2$
4a	260	91	51.58 51.60	4.73 4.69	14.74 15.04	$C_{12}H_{13}N_3O_3S$
4b	183	94	54.95 54.87	3.53 3.68	16.56 17.06	$C_{15}H_{12}N_4O_3S$
4c	220	88	50.80 50.81	4.19 4.26	13.14 13.67	$C_{13}H_{13}N_3O_4S$
4d	290	81	45.37 45.36	3.09 3.11	24.33 24.04	$C_{11}H_9N_5O_3S$
4e	178	83	51.55 51.64	2.97 3.06	11.01 10.63	$C_{17}H_{12}F_3N_3O_3S$
4f	226	80	58.67 58.66	3.73 3.69	10.03 10.26	$C_{20}H_{15}N_3O_3S_2$
4g	147	68	43.35 43.24	3.07 3.02	12.87 12.61	$C_{12}H_{10}F_3N_3O_3S$
4h	240	87	53.28 53.23	5.13 5.15	14.81 14.32	$C_{13}H_{15}N_3O_3S$
4i	225	82	56.16 56.06	5.88 5.96	12.73 13.07	$C_{15}H_{19}N_3O_3S$
4j	144	85	61.86 61.77	5.25 5.18	12.06 11.37	$C_{19}H_{19}N_3O_3S$
4k	138	69	56.41 56.41	5.37 5.37	13.16 13.16	$C_{15}H_{17}N_3O_3S$
5a	337	—	55.13 55.16	4.19 4.24	15.73 16.08	$C_{12}H_{11}N_3O_2S$
5b	>360	—	57.93 58.05	3.17 3.25	17.37 18.05	$C_{15}H_{10}N_4O_2S$
5c	330	—	53.89 53.97	3.71 3.83	14.06 14.52	$C_{13}H_{11}N_3O_3S$
5d	>360	—	48.29 48.35	2.63 2.58	25.77 25.63	$C_{11}H_7N_5O_2S$
5e	277	—	54.03 54.11	2.75 2.67	10.85 11.14	$C_{17}H_{10}F_3N_3O_2S$
5f	343	—	61.45 61.36	3.26 3.35	11.04 10.73	$C_{20}H_{13}N_3O_2S_2$
5g	282	—	45.59 45.72	2.39 2.56	12.79 13.33	$C_{12}H_8F_3N_3O_2S$
5h	298	—	56.69 56.71	4.79 4.76	15.57 15.26	$C_{13}H_{13}N_3O_2S$
5i	315	—	59.27 59.38	5.60 5.65	14.19 13.85	$C_{15}H_{17}N_3O_2S$
5j	268	—	65.02 64.94	4.77 4.88	11.69 11.96	$C_{19}H_{17}N_3O_2S$
5k	148	—	59.82 59.78	4.98 5.02	14.23 13.94	$C_{15}H_{15}N_3O_2S$

by either precipitation or recrystallization from 95% EtOH if necessary.

N*-(Thieno[2,3-*b*]pyridin-2-ylcarbonyl)-α-amino acids (4a—k) (general procedure).** ***A. A 10% aqueous KOH solution (16 mL) and *N*-chloroacetyl-α-amino acid **1** (10 mmol) were added to a solution of pyridinethione **2** (10 mmol) in DMF (10 mL) at 20 °C. The reaction mixture was stirred at 50 °C for 8 and 12 h in the case of alkyl-substituted pyridinethiones and pyridinethiones containing aromatic and heteroaromatic substituents, respectively. The reaction mixture was cooled and acidified with 10% HCl to Congo red. Then water (25 mL) was added. The precipitate that formed was filtered off and purified by either precipitation or recrystallization from 95% EtOH if necessary.

B. A 10% aqueous KOH solution (5 mL) was added to a solution of *N*-acyl-α-amino acid **3** (10 mmol) in DMF (10 mL) at 20 °C and stirred at 50 °C for 7 and 12 h in the case of alkyl-substituted compounds and compounds containing aromatic and heteroaromatic substituents, respectively. Then the reaction mixture was treated as described in the method *A*.

3,4-Dihydropyrido[3′,2′:4,5]thieno[3,2-*e*][1,4]diazepine-2(1*H*),5-diones (5a—k). *N*-Acyl-α-amino acids **4** (1 mmol) were heated to 220 °C without a solvent and kept at this temperature for 1 h. Analytically pure products were prepared in virtually quantitative yields (96—98%). The optical activity was measured for the samples recrystallized from aqueous DMSO.

The spectroscopic characteristics of diazepine-2,5-diones **5** are given in Table 3. The results of elemental analysis are presented in Table 4.

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