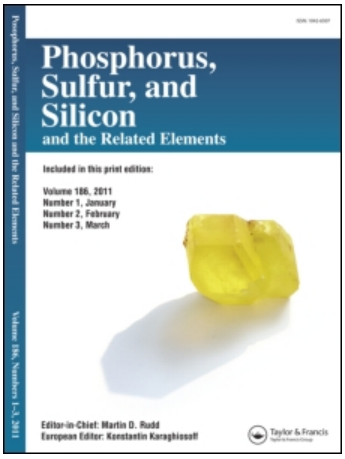

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Synthesis and Reactivity of 2-(1,2,3-Dithiazol-5- Ylidene)Aminothiophenes

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SYNTHESIS AND REACTIVITY OF 2-(1,2,3-DITHIAZOL-5-YLIDENE)AMINOTHIOPHENES

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The reaction of aminothiophenes (1) with Appel's salt (2) affords 2-(1,2,3-dithiazol-5-ylidene)aminothiophenes (3). Under the action of $ZnCl_2$, the latter compounds are transformed into 1,3-oxazin-4-one systems (4). The reactions of compounds 4 with dienophiles under atmospheric or high pressure give thienopyridines (6–11); the reactions with amines produce pyrimidinones (12) and guanidines (14–15).

Keywords Aminothiophenes; cycloaddition; 1,2,3-dithiazolimines; high pressure; thienopyridines

INTRODUCTION

1,2,3-Dithiazole derivatives are widely used in the synthesis of various compounds having useful properties.[1] 1,2,3-Dithiazolimines prepared by the reaction of amines with 4,5-dichloro-1,2,3-dithiazolium chloride (Appel's salt) are of great interest for the synthesis of biologically active compounds.[2, 3] Earlier, we developed procedures for the synthesis of the previously unknown 1,2,3-dithiazolimines and used these reaction products for the synthesis of various heterocyclic compounds.[4, 5] 1,2,3-Dithiazoimines prepared from anthranilic acid derivatives have great synthetic potential. These compounds can be transformed into 2-cyano-3,1-benzoxazin-4-ones or 2-cyano-3,1-benzothiazin-4-ones, quanazolin-4-ones, and 4-alkoxypyrimidines.[6] Some reactions with heteroaromatic analogs also are known.[2,6,7]

In the present study, we synthesized the previously unknown 2-(1,2,3-dithiazol-5-ylidene)aminothiophenes and transformed these compounds into the reactive 1,3-azin-4-one systems, which are of interest in the synthesis of various compounds, including thienopyridines. Fused pyridine derivatives are known to be involved in many natural compounds and are widely used in the synthesis of various biologically active compounds.[8]

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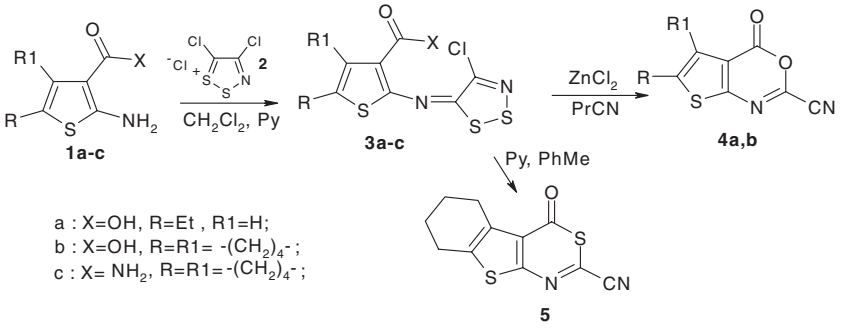
RESULTS AND DISCUSSION

2-(1,2,3-Dithiazol-5-ylidene)aminothiophenes were synthesized starting from 2-aminothiophene-3-carboxylic acid derivatives, which were prepared by the Gewald reaction. Carboxylic acids **1a**,**b** were synthesized by saponification of the corresponding ethyl esters.

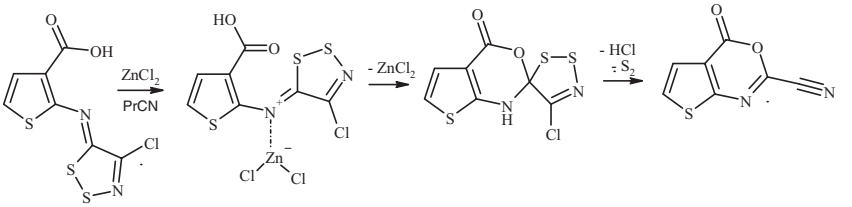
2-(1,2,3-Dithiazol-5-ylidene)aminothiophenes **3a–c** were prepared in good yields by the slow addition of a two- or threefold excess of pyridine to a mixture of 2-aminothiophene-3-carboxylic acid derivatives **1a–c** and Appel's salt **2** pre-stored in anhydrous dichloromethane or a dichloromethane–tetrahydrofuran mixture at room temperature for 30 min (Scheme 1).



Scheme 1 Synthesis of 2-(1,2,3-dithiazol-5-ylidene)aminothiophenes **3a–c**, 1,3-oxazines **4a**,**b**, and 1,3-thiazine **5**.

By analogy with the published data, oxazines **4a**,**b** would be expected to be formed by refluxing acids **3a**,**b** in toluene[9] or in the presence of bases;[10] thiazine **5** would be expected to be produced in the reaction of amide **3c** with triphenyl phosphine.[9] However, our attempts to perform the required transformations according to the methods described in the literature failed. In these reactions, either the starting compounds remained unconsumed or multicomponent systems were obtained.

We found that acids rather than bases proved to be efficient catalysts for the reaction giving rise to oxazines **4a**,**b** (Scheme 2, for some mechanistic aspects see refs.[1,7,11]). We investigated the influence of various Lewis acids and solvents (toluene, xylene, acetonitrile, and butyronitrile) on the reaction pathway. Actually, we found that 1,2,3-dithiazolimines **3a**,**b** were transformed into the corresponding thieno[2,3-d]-1,3-oxazin-4-ones **4a**,**b** by refluxing in the presence of $AlCl_3$, $SnCl_4$, $TiCl_4$, $ZnCl_2$, or $BF_3{\cdot}Et_2O$ (Scheme 1). The



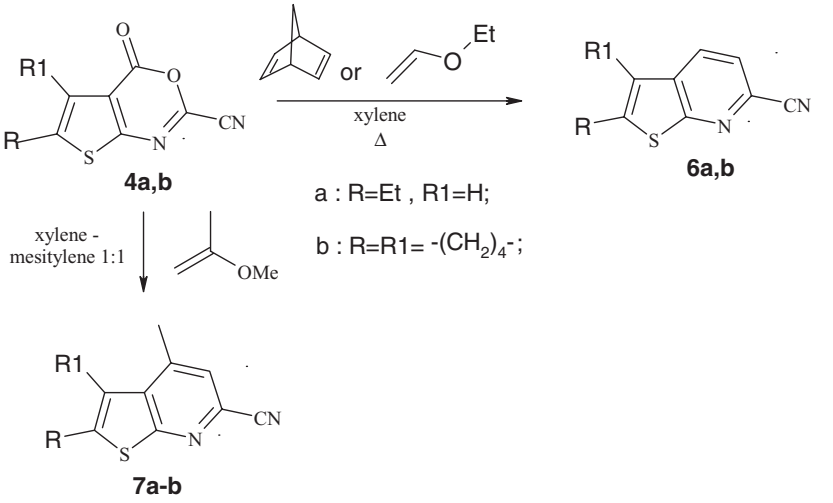
Scheme 2 Possible scheme of the transformation of 1,2,3-dithiazolimines **3** into 2-cyano-1,3-oxazin-4-ones **4** in the presence of $ZnCl_2$.

highest yields of oxazin-4-ones (86–98%) were achieved in the presence of $ZnCl_2$ in butyronitrile.

The cyclization of amide **3c** to 2-cyano-5,6-tetramethylenethieno[2,3-d]thiazin-4-one **5,** occurs in the presence of pyridine in boiling toluene (Scheme 1).

We studied the reactions of 2-cyanothieno[2,3-d]-1,3-oxazin-4-ones **4a**,**b** with dienophiles and amines. Oxazin-4-ones **4a**,**b** contain the latent 2-azadiene system and, therefore, can be involved in the [4+2]-cycloaddition reaction with various dienophiles.

We found that dienes **4a**,**b** are readily involved in the Diels–Alder reaction with 2,5-norbornadiene or ethyl vinyl ether in boiling xylene to form 6-cyanothieno[2,3-b]pyridines **6a**,**b**; the reactions with 2-methoxypropene afford 6-cyanothieno[2,3-b]pyridines **7a**,**b**. However, in the latter case, the [4+2]-cycloaddition reactions proceed under more drastic conditions compared to the reactions with ethyl vinyl ether due, apparently, to steric hindrance of the methyl group in 2-methoxypropene (Scheme 3).



Scheme 3 Transformation of 2-cyano-1,3-oxazin-4-ones **4** into thienopyridines **6** and **7**.

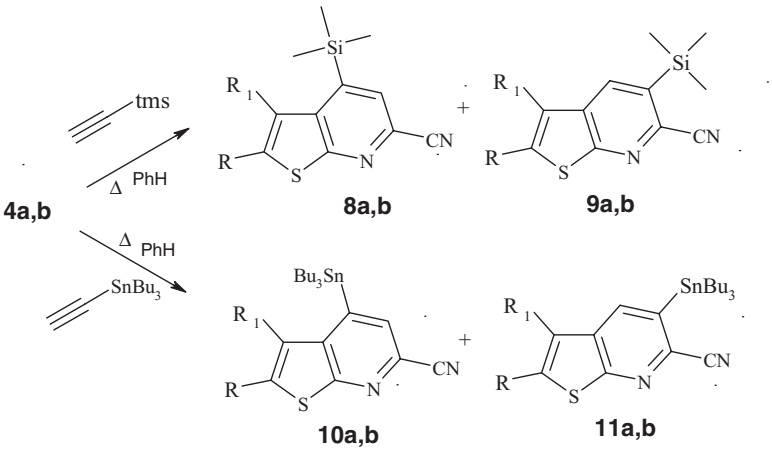
In the reactions in the presence of Lewis acids ($BF_3 \cdot Et_2O$ or $ZnCl_2$) as the catalysts at temperatures from 0°C to 120°C, either the starting compounds underwent substantial polymerization or the starting 2-cyanothieno[2,3-d]-1,3-oxazin-4-one remained intact.

We examined the possibility of using trimethylsilylacetylene and tributyltin acetylene as dienophiles. It should be noted that the reactions of oxazinones with these reagents have not been previously reported. The introduction of the trimethylsilyl or tributylstannyl groups into the pyridine ring greatly extends the scope of further functionalizations of pyridines with electrophiles or under the cross-coupling conditions.

However, the reactions of 2-cyanothieno[2,3-d]-1,3-oxazin-4-ones **4a**,**b** with excess of trimethylsilylacetylene as the dienophile in boiling mesitylene proceeded very slowly and afforded insignificant amounts trimethylsilylthieno[2,3-b]pyridines even after 72 h.

The published data[12] and our experimental results,[13] including the data on the reactions with 1,2,3-dithiazolimines,[5] show that the reaction rate of cycloaddition substantially increases under high pressure.

Actually, the Diels–Alder reaction of thieno[2,3-d]-1,3-oxazin-4-ones **4a**,**b** at high pressure (10 kbar) proceeded much more rapidly and afforded the corresponding trimethylsilylthieno[2,3-b]pyridines **8–9a**,**b** in high yields (Scheme 4). An analysis of the ^{1}H NMR spectra shows that thieno[2,3-b]pyridines are formed as mixtures of isomers with respect to the position of the trimethylsilyl group. The reaction of compound **4a** affords isomers **8a** and **9a** in a ratio of 7.3:1, whereas the reaction of **4b** gives isomers **8b** and **9b** in an inverse ratio (1:3.2). The formation of isomers **8a** and **8b** is attributed to the electronic requirements of the Diels–Alder reaction, whereas the formation of isomers **9a** and **9b** is controlled by the steric factors. In the case of compounds **8,9b**, the ratio of the isomers depends on the steric effects of the alkyl chain at position 4.



Scheme 4 Synthesis of trimethylsilylthieno[2,3-b]pyridines **8** and **9** and tributyltin derivatives of thieno[2,3-b]pyridines **10** and **11**.

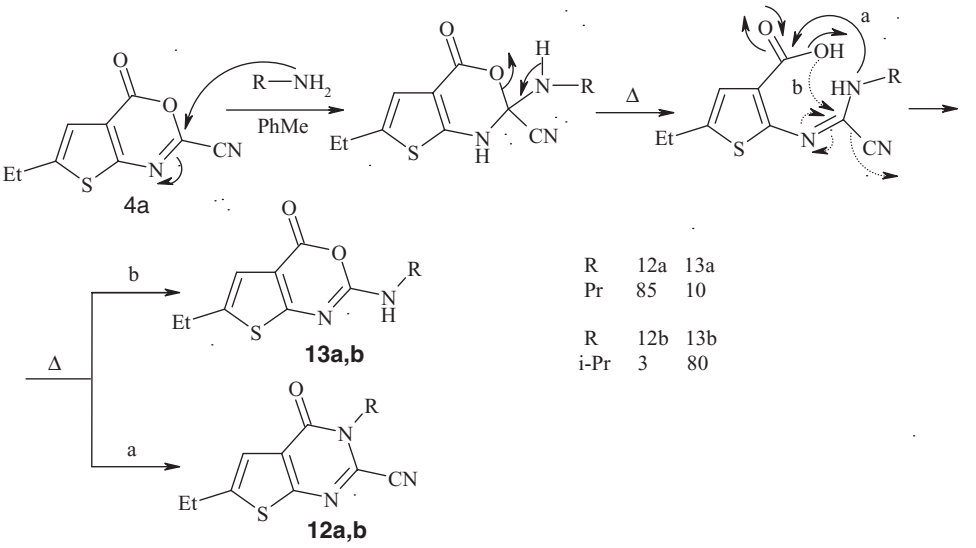
The Diels–Alder reaction of compounds **4a**,**b** with tributyltin acetylene at high pressure also produced tributyltin derivatives of thieno[2,3-b]pyridines **10** and **11** in high yields (Scheme 4). The introduction of the bulkier Bu_3Sn group even into sterically less hindered 1,3-oxazin-4-one **4a** leads to an inversion of the ratio of the isomers (as compared to the tetramethylsilyl group), resulting in the formation of **11b** as the major isomer. It should be noted that this reaction, like the reaction of trimethylsilylacetylene, proceeds at a low rate under atmospheric pressure in boiling mesitylene.

It is known that 1,3-oxazin-4-ones readily react with primary amines, resulting in the formation of linear products accompanied by the opening of the oxazine-4-one ring, as well as the formation of pyrimidin-4-ones.[1,14]

We showed that primary amines most readily react with 1,3-oxazin-4-ones if the reactions are initially performed at room temperature in toluene with an equivalent amount of amine for 30 min followed by refluxing for 2 h.

The reaction of thieno[2,3-d]-1,3-oxazin-4-one **4a** with *n*-propylamine in toluene afforded thieno[2,3-d]pyrimidin-4-one **12a** in 85% yield (Scheme 5). 6-Ethyl-2-(propylamino)thieno[2,3-d]-1,3-oxazin-4-one **13a** was detected as the byproduct (10%).

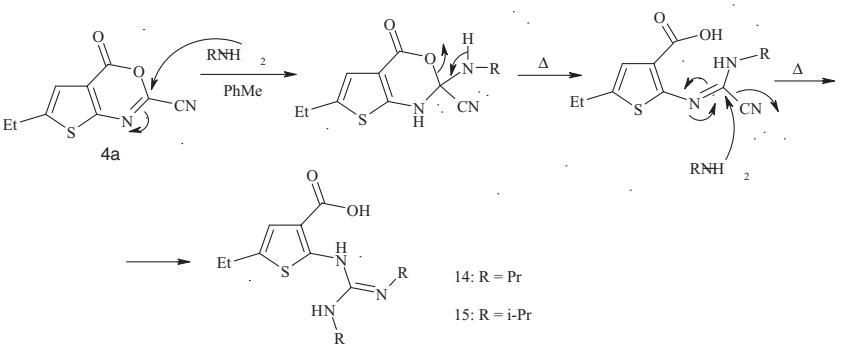
Under analogous conditions, the reaction of **4a** with isopropylamine in toluene produces 6-ethyl-2-(isopropylamino)thieno[2,3-d]-1,3-oxazin-4-one **13b** as the major product along with a small amount of 2-cyano-6-ethyl-3-isopropylthieno[2,3-d]pyrimidin-4-one



Scheme 5 Synthesis of thieno[2,3-d]-pyrimidin-4-ones **12** and thieno[2,3-d]-1,3-oxazin-4-ones **13**.

12b (Scheme 5). The proposed scheme of the reaction involves the initial nucleophilic attack of amine on the imine carbon atom followed by heterocyclization. A substantial structural difference between the reaction products is apparently associated with the steric hindrance of the bulky isopropylamino group (path a). As a result, the reaction follows the alternative pathway (path b) involving the nucleophilic attack of the carboxy group of the cyanoamide carbon atom on the OH group to form thieno[2,3-d]-1,3-oxazin-4 -one.

Under analogous conditions, the reaction with the use of excess propyl- or isopropylamine produces [N-(3-carboxy-5-ethylthienyl-2)]-N′,N″-bis(propyl)guanidine **14** and [N-(3-carboxy-5-ethylthienyl-2)]-N′,N″-bis(isopropyl)guanidine **15** (Scheme 6). The possible scheme of this reaction involves the initial attack of amine on the carbon atom of 1,3-oxazin-4-one **4a** to form [N-(3-carboxy-5-ethylthienyl-2)]-N′-alkylcyanoamidines. The reaction of the latter compounds with the second equivalent of the primary amine affords the target compounds as a result of the nucleophilic substitution of the CN group (Scheme 6).



Scheme 6 Transformation of 1,3-oxazin-4-one into guanidines **14**,**15**.

Hence, we developed procedures for the synthesis of thiophene-containing dithiazolimines and showed that these compounds can be transformed into various linear and heterocyclic structures.

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were measured on a Bruker AC-200 (200 and 50.32 MHz for ^1H and ^{13}C, respectively) and Bruker AM-300 (300.13 and 75.47 MHz for ^1H and ^{13}C, respectively) instruments in DMSO-d_6 and $CDCl_3$ with $SiMe_4$ as the internal standard. The chemical shifts are given in ppm relative to $SiMe_4$ with an accuracy of 0.01 ppm. The mass spectra were obtained on a Varian MAT CH-6 instrument using a direct inlet system; the ionization energy was 70 eV; the accelerating voltage was 1.75 kW. The IR spectra were recorded on a Specord M-82 instrument in KBr pellets. The melting points were measured on a Boetius hot-stage apparatus. All reactions mixtures were analyzed, and the purity of the reaction products was checked by TLC on silica gel 60 F_{254} plates (Merck); the spots were visualized with an acidified $KMnO_4$ solution, iodine vapor, or under UV light. The preparative chromatography was carried out on silica gel columns (63–200 mesh, Merck). All solvents and the starting compounds were purified immediately before use according to standard procedures. The high-pressure synthesis was performed in Teflon tubes on an apparatus described earlier.[15]

The starting compounds were synthesized according to known procedures: 2-amino-5-ethylthiophene-3-carboxylic acid (**1a**),[16] 2-amino-4,5-tetramethylenethiophene-3-carboxylic acid (**1b**),[16] 2-amino-4,5-tetramethylenethiophene-3-carboxamide (**1c**),[16] and 4,5-dichloro-1,2,3-dithiazolium chloride (Appel's salt) (**2**).[17]

General Procedure for the Synthesis of Compounds 3a,b

Compound **1a** (1.000 g, 0.0058 mol) or **1b** (1.000 g, 0.005 mol) and anhydrous dichloromethane (90 mL) were placed in a 150-mL flask equipped with a magnetic stirrer. Then Appel's salt (**2**) (1.057 g, 0.005 mol) was slowly added with stirring. Within 30 min after the addition of salt **2**, pyridine (1.225 mL, 0.0153 mol) was added dropwise with stirring. The reaction mixture was stirred at room temperature for 1.5 h. Then dichloromethane was evaporated on a rotary evaporator, and the residue was purified by column chromatography (silica gel; petroleum ether and then CH_2Cl_2 as the eluents).

2-(4-[Chloro-5H-1,2,3-dithiazol-5-ylidene]amino)-5-ethylthiophene-3-carboxylic acid (3a). The yield was 1.364 g (76%); dark red solid; mp 204°C. ^1H NMR (300.13 MHz, DMSO-d_6, 24°C), δ: 1.28 (t, 3H, $-C-\underline{CH_3}$), 2.88 (q, 2H, $-\underline{CH_2}-CH_3$), 7.25 (s, 1H, H (th-4)). ^{13}C NMR (75.47 MHz, DMSO-d_6, 24°C), δ: 15.13 ($5-C-\underline{CH_3}$), 23.15 ($5-\underline{CH_2}-C$), 125.06 (CH (th-4)), 141.79 (C (th-5)), 146.31 ($\underline{C}-COOH$ (th-3)), 150.72 ($Cl-\underline{C}=N$), 156.96 ($\underline{C}-N$ = (th-2)), 162.29 ($N=\underline{C}-S$), 164.47 (COOH). MS (70 eV), *m/z*: 306 $[M]^+$, 291 $[M-CH_3]^+$, 273 $[M-CH_3-OH]^+$, 242 $[M-S_2]^+$, 226 $[M-Cl-COOH]^+$, 206 [M (**4a**)]$^+$, 198 $[M-S_2-COOH]^+$, 191 [M (**4a**)$-CH_3]^+$, 180 [M (**4a**)$-CN]^+$, 166 [M (**4a**)$-CH_3-CN]^+$. Analysis for $C_9H_7ClN_2O_2S_3$ (306.82): Calcd.: C, 35.23; H, 2.30; N, 9.13; S, 31.35%. Found: C, 35.26; H, 2.26; N, 9.14; S, 31.32%.

2-(4-[Chloro-5H-1,2,3-dithiazol-5-ylidene]amino)-4,5-tetramethylenethiophene-3-carboxylic acid (3b). The yield was 0.930 g (55%); dark red solid; mp 214°C. ^1H NMR (300.13 MHz, DMSO-d_6, 24°C), δ: 1.65–1.91 (m, 4H, $-C-\underline{CH_2}-\underline{CH_2}-C-$ (CHex)), 2.58–2.93 (m, 4H, $-\underline{CH_2}-C-C-\underline{CH_2}-$ (CHex)), 12.33–12.52 (s, 1H, COOH).

^{13}C NMR (75.47 MHz, DMSO-d_6, 24°C), δ: 22.32 (5−C−$\underline{CH_2}$−C−C−4), 22.54 (5−C−C−$\underline{CH_2}$−C−4), 23.71 (5−$\underline{CH_2}$−C−C−C−4), 25.56 (4−$\underline{CH_2}$−C−C−C−5), 126.87 (C (th-5)), 137.51 (C (th-4)), 139.10 ($\underline{C}$−COOH (th-3)), 148.49 ($\underline{C}$−N = (th-2)), 151.21 (Cl−$\underline{C}$=N), 154.88 (N=$\underline{C}$−S), 165.52 (COOH). MS (70 eV), *m/z*: 332 $[M]^+$, 314 $[M-H_2O]^+$, 279 $[M-Cl-OH]^+$, 268 $[M-S_2]^+$, 232 [M (**4 b**)]$^+$, 206 [M (**4 b**)−CN]$^+$, 204 [M (**4 b**)−C_2H_4]$^+$, 178 [M (**4 b**)−C_2H_4−CN]$^+$, 176 [M (**4 b**)−$2C_2H_4$]$^+$. Analysis for $C_{11}H_9ClN_2O_2S_3$ (332.86): Calcd.: C, 39.69; H, 2.73; N, 8.42; S, 28.90%. Found: C, 39.72; H, 2.79; N, 8.67; S, 28.94%.

2-(4-[Chloro-5H-1,2,3-dithiazol-5-ylidene]amino)-4,5-tetramethylenethiophene-3-carboxamide (3c)

Compound **1c** (1.000 g, 0.0051 mol) and anhydrous dichloromethane (90 mL) were placed in a 150-mL flask equipped with a magnetic stirrer. Then Appel's salt (**2**) (1.062 g, 0.0051 mol) was slowly added with stirring. Within 30 min after the addition of salt **2**, pyridine (1.231 mL, 0.0153 mol) was added dropwise with stirring. The reaction mixture was stirred at room temperature for 1.5 h. Then dichloromethane was removed on a rotary evaporator, and the residue was purified by column chromatography (silica gel; gradient elution with CH_2Cl_2—EtOAc : CH_2Cl_2 (1:1)). The yield was 1.020 g (60%); red solid; mp 195–196°C. ^{1}H NMR (200.13 MHz, DMSO-d_6, 24°C), δ: 1.65–1.90 (m, 4H, −C−$\underline{CH_2}$−$\underline{CH_2}$−C− (CHex)), 2.78–2.93 (m, 4H, −$\underline{CH_2}$−C−C−$\underline{CH_2}$− (CHex)), 7.32 and 8.20 (s, 2H, J_{HH} = 175.8 Hz, NH_2). ^{13}C NMR (50.32 MHz, DMSO-d_6, 40°C), δ: 21.81 (4−C−$\underline{CH_2}$−C−C−5), 22.29 (4−C−C−$\underline{CH_2}$−C−5), 24.86 (5−$\underline{CH_2}$−C−C−C−4), 26.07 (4−$\underline{CH_2}$−C−C−C−5), 128.77 (C (th-5)), 131.98 (C (th-4)), 137.20 ($\underline{C}$−$CONH_2$ (th-3)), 146.19 ($\underline{C}$−N= (th-2)), 146.71 (Cl−$\underline{C}$=N), 152.79 (N=$\underline{C}$−S), 164.29 ($CONH_2$). MS (70 eV), *m/z*: 331 $[M]^+$, 314 $[M-NH_2]^+$, 279 $[M-Cl,-NH_2]^+$, 265 $[M-S_2]^+$, 251 $[M-S_2-NH_2]^+$, 232 $[M-S_2-Cl]^+$, 204 $[M-S_2-Cl-C_2H_4]^+$, 176 $[M-S_2-Cl-2C_2H_4]^+$. Analysis for $C_{11}H_{10}ClN_3OS_3$ (331.87): Calcd.: C, 39.81; H, 3.04; N, 12.66; S, 28.99%. Found: C, 39.79; H, 3.07; N, 12.67; S, 28.95%.

General Procedure for the Synthesis of Compounds 4a,b

Imine **3a** (0.005 mol, 1.530 g) or **3b** (0.005 mol, 1.660 g) and butyronitrile (200 mL) were placed in a 250-mL flask equipped with a reflux condenser with a calcium chloride tube and a magnetic stirrer. The reaction mixture was heated with stirring until the imine was dissolved. Then anhydrous $ZnCl_2$ (2.044 g, 0.015 mol) was added with stirring. The reaction mixture was refluxed with stirring for 6 h, anhydrous $ZnCl_2$ (0.681 g, 0.005 mol) being added at 1-h intervals. Then the reaction mixture was cooled, diluted with petroleum ether (200 mL), and filtered through a layer of silica gel. The solvent was distilled off on a rotary evaporator, and the residue was purified by column chromatography (silica gel; petroleum ether:EtOAc, 3:1 as the eluent).

2-Cyano-6-ethylthieno[2,3-d]1,3-oxazin-4-one (4a). The yield was 0.890 g (86%); white solid; mp 89–91°C. IR (KBr), ν (cm^{-1}): 2252.0 (−C≡N), 1784.0 (C=O). ^{1}H NMR (200.13 MHz, $CDCl_3$, 24°C), δ: 1.40 (t, 3H, −C−CH_3), 2.97 (q, 2H, −CH_2−CH_3), 7.26 (s, 1H, H (th-4)). ^{13}C NMR (50.32 MHz, $CDCl_3$, 24°C), δ: 15.25 (5−C−$\underline{CH_3}$), 24.27

(5−$\underline{CH_2}$−C), 110.22 (CN), 119.61 (CH (th-4)), 122.21 (C (th-5)), 135.06 ($\underline{C}$−C(O)O− (th-3)), 151.79 ($\underline{C}$−CN), 152.79 (S−$\underline{C}$−N (th-2)), 157.96 (−$\underline{C}$(O)O−). MS (70 eV), *m/z*: 206 $[M]^+$, 191 $[M- CH_3]^+$, 180 $[M-CN]^+$, 177 $[M- C_2H_5]^+$, 163 $[M-CH_3-CO]^+$, 151 $[M-C_2H_5-CN]^+$, 124 $[M-C(O)OCCN]^+$, 109 $[M-C(O)OCCN-CH_3]^+$. Analysis for $C_9H_6N_2O_2S$ (206.23): Calcd.: C, 52.42; H, 2.93; N, 13.58; S, 15.55%. Found: C, 52.44; H, 2.90; N, 13.60; S, 15.56%.

2-Cyano-5,6,7,8-tetrahydro[1]benzo[2,3-d]1,3-oxazin-4-one (4b). The yield was 1.137 g (98%); white solid; mp 111°C. ^{1}H NMR (200.13 MHz, $CDCl_3$, 24°C), δ: 1.82–1.99 (m, 4H, −C−$\underline{CH_2}$−$\underline{CH_2}$−C− (CHex)), 2.85–2.97 (m, 4H, −$\underline{CH_2}$−C−C−$\underline{CH_2}$− (CHex)). ^{13}C NMR (50.32 MHz, $CDCl_3$, 24°C), δ: 21.72 (5−C−$\underline{CH_2}$−C−C−4), 22.56 (5−C−C−$\underline{CH_2}$−C−4), 25.12 (5−$\underline{CH_2}$−C−C−C−4), 25.51 (4−$\underline{CH_2}$−C−C−C−5), 110.33 (CN), 120.36 (C (th-5)), 133.95 (C (th-4)), 134.75 ($\underline{C}$−C(O)O− (th-3)), 141.46 ($\underline{C}$−CN), 151.96 (S−$\underline{C}$−N (th-2)), 157.37 (−$\underline{C}$(O)O−). MS (70 eV), *m/z*: 232 $[M]^+$, 204 $[M- C_2H_4]^+$, 178 $[M-C_2H_4-CN]^+$, 176 $[M- 2C_2H_4]^+$, 150 $[M-2C_2H_4-CN]^+$, 150 $[M-C(O)OCCN]^+$. Analysis for $C_{11}H_8N_2O_2S$ (232.07): Calcd.: C, 56.88; H, 3.47; N, 12.06; S, 13.81%. Found: C, 56.84; H, 3.49; N, 12.10; S, 13.76%.

2-Cyano-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]1,3-thiazin-4-one (5)

Compound **3c** (1.000 g, 0.003 mol) and toluene (50 mL) were placed in a 100-mL flask equipped with a reflux condenser with a calcium chloride tube. The reaction mixture was heated with stirring until the imine (**3c**) was dissolved. Then pyridine (0.725 mL, 0.009 mol) was added. The reaction mixture was refluxed for 4 h and cooled. The solvent was distilled off on a rotary evaporator, and the residue was purified by column chromatography (silica gel; petroleum ether:EtOAc, 3:1 as the eluent). The yield was 0.261 g (35%); white solid; mp 109–110°C. ^{1}H NMR (300.13 MHz, $CDCl_3$, 24°C), δ: 1.85–1.99 (m, 4H, −C−$\underline{CH_2}$−$\underline{CH_2}$−C− (CHex)), 2.89–3.04 (m, $^3J_{HH}$ = 5.15 Hz, $^3J_{HH}$ = 5.14 Hz, 4H, −$\underline{CH_2}$−C−C−$\underline{CH_2}$− (CHex)). ^{13}C NMR (75.47 MHz, $CDCl_3$, 24°C), δ: 21.95 (5−C−$\underline{CH_2}$−C−C−4), 22.29 (5−C−C−$\underline{CH_2}$−C−4), 25.66 (5−$\underline{CH_2}$−C−C−C−4), 26.36 (4−$\underline{CH_2}$−C−C−C−5), 113.19 (CN), 122.67 (C (th-5)), 130.93 (C (th-3)), 135.90 (C (th-4)), 142.07 ($\underline{C}$−CN), 160.76 (S−$\underline{C}$−N (th-2)), 173.34 (−$\underline{C}$(O)S−). MS (70 eV), *m/z*: 248 $[M]^+$, 220 $[M- C_2H_4]^+$, 192 $[M-C_2H_4-CO]^+$, 166 $[M- C_2H_4-CO-CN]^+$, 150 $[M-C(O)SCCN]^+$, 134 $[M-2C_2H_4-CN-S]^+$, 122 $[M-C(O)SCCN-C_2H_4]^+$. Analysis for $C_{11}H_8N_2OS_2$ (248.32): Calcd.: C, 53.20; H, 3.25; N, 11.28; S, 25.83%. Found: C, 53.14; H, 3.29; N, 11.26; S, 25.74%.

General Procedures for the Synthesis of Compounds 6a,b

Method A: Compound **4a** (0.200 g, 0.971 mmol) or **4b** (0.200 g, 0.862 mmol), norbornadiene (0.893 g, 9.71 mmol), and xylene (4 mL) were placed in a 30-mL flask equipped with a reflux condenser. The reaction mixture was refluxed for 48 h. In all methods, the reaction mixture was then cooled, the solvent was distilled off on a rotary evaporator, and the residue was purified by preparative thin-layer chromatography (silica gel; petroleum ether:EtOAc, 3:1 as the eluent).

Method B: Compound **4a** (0.200 g, 0.971 mmol) or **4b** (0.200 g, 0.862 mmol), ethyl vinyl ether (2.097 g, 29.13 mmol), and xylene (5 mL) were placed in a 30-mL flask equipped with a reflux condenser. The reaction mixture was refluxed for 48 h.

Method C: A mixture of **4a** (0.100 g, 0.486 mmol) or **4b** (0.100 g, 0.431 mmol) and ethyl vinyl ether (0.349 g, 4.86 mmol) in benzene (1.5 mL) was kept at 10 kbar and 160°C for 7 h.

6-Cyano-2-ethylthieno[2,3-b]pyridine (6a). The yields according to method A was 0.141 g (77%); method B, 0.137 g (75%); method C, 0.088 g (96%);white solid; mp 88°C. IR (KBr), ν (cm^{-1}): 2240.0 (−C≡N). ^{1}H NMR (300.13 MHz, $CDCl_3$, 24°C), δ: 1.43 (t, 3H, −C−$\underline{CH_3}$), 3.01 (q, 2H, −$\underline{CH_2}$−CH_3), 7.04 (s, 1H, CH (th-4)), 7.60 (d, 1H, $^3J_{HH}$ = 7.96 Hz, CH (Py-3)), 7.99 (d, 1H, $^3J_{HH}$ = 7.96 Hz, CH (Py-4)). ^{13}C NMR (75.47 MHz, $CDCl_3$, 24°C), δ: 14.94 (5−C−$\underline{CH_3}$), 24.98 (5−$\underline{CH_2}$−C), 117.26 (CH (th-4)), 117.82 (CN), 123.62 (CH (Py-3)), 128.19 ($\underline{C}$−CN), 130.03 (CH (Py-4)), 136.15 (C (th-3)), 154.83 (C (th-5)), 161.91 (C (th-2)). MS (70 eV), *m/z*: 188 $[M]^+$, 173 $[M-CH_3]^+$, 147 $[M-CH_3-CN]^+$. Analysis for $C_{10}H_8N_2S$ (188.25): Calcd.: C, 63.80; H, 4.28; N, 14.88; S, 17.03%. Found: C, 63.72; H, 4.25; N, 14.82; S, 17.01%.

2-Cyano-5,6,7,8-tetrahydro[1]benzothieno[2,3-b]pyridine (6b). The yields according to method A was 0.157 g (85%); method B, 0.144 g (78%); method C, 0.090 g (98%);white solid; mp 102°C. ^{1}H NMR (300.13 MHz, $CDCl_3$, 24°C), δ: 1.96 (s, 4H, −C−$\underline{CH_2}$−$\underline{CH_2}$−C− (CHex)), 2.73–2.92 (d, 4H, −$\underline{CH_2}$−C−C−$\underline{CH_2}$− (CHex)), 7.59 (d, 1H, $^3J_{HH}$ = 8.09 Hz, CH (Py-3)), 7.86 (d, 1H, $^3J_{HH}$ = 8.09 Hz, CH (Py-4)). ^{13}C NMR (50.32 MHz, $CDCl_3$, 24°C), δ: 21.93 (5−C−$\underline{CH_2}$−C−C−4), 23.05 (5−C−C−$\underline{CH_2}$−C−4), 23.14 (5−$\underline{CH_2}$−C−C−C−4), 26.09 (4−$\underline{CH_2}$−C−C−C−5), 117.93 (CN), 123.33 (CH (Py-3)), 127.80 (CH (Py-4)), 133.93 (C (th-4)), 135.61 ($\underline{C}$−CN), 139.29 (C (th-5)), 143.72 (C (th-3)), 161.52 (C (th-2)). MS (70 eV), *m/z*: 214 $[M]^+$, 186 $[M-C_2H_4]^+$, 160 $[M-C_2H_4-CN]^+$. Analysis for $C_{12}H_{10}N_2S$ (214.29): Calcd.: C, 67.26; H, 4.70; N, 13.07; S, 14.96%. Found: C, 67.31; H, 4.75; N, 13.11; S, 15.01%.

General Procedures for the Synthesis of Compounds 7a,b

Method A: Compound **4a** (0.200 g, 0.971 mmol), 2-methoxypropene (2.797 g, 38.84 mmol), and a 1:1 xylene:mesitylene mixture (4 mL) were placed in a 30-mL flask equipped with a reflux condenser. The reaction mixture was refluxed for 48 h. In all methods, the reaction mixture was then cooled, the solvent was distilled off on a rotary evaporator, and the residue was purified by preparative thin-layer chromatography (silica gel; petroleum ether:EtOAc, 3:1 as the eluent).

Method B: A mixture of **4a** (0.100 g, 0.486 mmol) and 2-methoxypropene (0.349 g, 4.86 mmol) in benzene (1.5 mL) was kept at 10 kbar and 160°C for 7 h.

6-Cyano-2-ethyl-4-methylthieno[2,3-b]pyridine (7a). The yield according to method A was 0.104 g (53%); method B, 0.092 g (94%); white solid; mp 91°C. ^{1}H NMR (300.13 MHz, $CDCl_3$, 24°C), δ: 1.42 (t, 3H, −C−$\underline{CH_3}$), 2.61 (s, 3H, CH_3 (Py-4)), 3.01 (q, 2H, −$\underline{CH_2}$−CH_3), 7.07 (s, 1H, CH (th-4)), 7.41 (s, 1H, CH (Py-3)). ^{13}C NMR (75.47 MHz, $CDCl_3$, 24°C), δ: 15.09 (5−C−$\underline{CH_3}$), 19.12 (CH_3 (Py-4)), 25.06 (5−$\underline{CH_2}$−C), 115.51 (CH (th-4)), 117.96 (CN), 124.38 (CH (Py-3)), 128.28 ($\underline{C}$−CN), 136.17 (C (Py-4)), 141.55 (C (th-3)), 153.71 (C (th-5)), 161.49 (C (th-2)). MS (70 eV), *m/z*: 202 $[M]^+$, 187 $[M-CH_3]^+$, 176 $[M-CN]^+$, 146 $[M-2CH_3-CN]^+$. Analysis for $C_{11}H_{10}N_2S$ (202.28): Calcd.: C, 65.32; H, 4.98; N, 13.85; S, 15.85%. Found: C, 65.40; H, 4.96; N, 13.81; S, 15.91%.

2-Cyano-4-methyl-5,6,7,8-tetrahydro[1]benzothieno[2,3-b]pyridine (7b). The yield according to method A was 0.128 g (65%); method B, 0.093 g (9%); white solid; mp 135–136°C. ^{1}H NMR (300.13 MHz, $CDCl_3$, 24°C), δ: 1.89–1.94 (m, 4H, −C−$\underline{CH_2}$−$\underline{CH_2}$−C− (CHex)), 2.73 (s, 3H, CH_3, (Py-4)), 2.92–3.03 (d,

4H, $-\underline{CH_2}-C-C-\underline{CH_2}-$ (CHex)), 7.31 (s, 1H, CH (Py-3)). ^{13}C NMR (75.47 MHz, $CDCl_3$, 24°C), δ: 20.77 (CH_3 (Py-4)), 22.38 (5−C−$\underline{CH_2}$−C−C−4), 22.74 (5−C−C−$\underline{CH_2}$−C−4), 26.46 (5−$\underline{CH_2}$−C−C−C−4), 27.12 (4−$\underline{CH_2}$−C−C−C−5), 117.90 (CN), 125.47 (CH (Py-3)), 127.80 (CH (th-4)), 128.53 ($\underline{C}$−CN), 134.88 (C (th-5)), 142.30 (C (Py-4)), 142.44 (C (th-3)), 161.25 (C (th-2)). MS (70 eV), *m/z*: 228 $[M]^+$, 213 $[M-CH_3]^+$, 200 $[M-C_2H_4]^+$, 187 $[M-CN-CH_3]^+$, 174 $[M-C_2H_4-CN]^+$. Analysis for $C_{13}H_{12}N_2S$ (228.31): Calcd.: C, 68.39; H, 5.30; N, 12.27; S, 14.04%. Found: C, 68.45; H, 5.22; N, 12.32; S, 14.00%.

General Procedure for the Synthesis of Compounds 8–11a,b

A mixture of diene **4a** (0.100 g, 0.486 mmol) or **4b** (0.100 g, 0.431 mmol) and (trimethylsilyl)acetylene (4.86 mmol, 0.476 g) or tributyltin acetylene (4.86 mmol, 1.529 g) as the dienophile in benzene (1.5 mL) was kept at 10 kbar and 160°C for 7 h. Then the solvent was distilled off on a rotary evaporator, and the residue was purified by preparative thin-layer chromatography (silica gel; petroleum ether:EtOAc, 6:1 as the eluent).

6-Cyano-2-ethyl-4-(trimethylsilyl)thieno[2,3-b]pyridine (8a) and 6-cyano-2-ethyl-5-(trimethylsilyl)thieno[2,3-b]pyridine (9a). The yield was 0.107 g (**8a**:**9a** = 7.3:1) (85%); white solid. ^1H NMR (300.13 MHz, $CDCl_3$, 24°C), δ: 0.44 (s, 9H, $Si(CH_3)_3$, **8a**), 0.49 (s, 9H, $Si(CH_3)_3$, **9a**), 1.43 (t, 3H, 5−C−$\underline{CH_3}$, **8a** and **9a**), 3.03 (q, 2H, 5−$\underline{CH_2}$−CH_3 **8a** and **9a**), 7.02 (s, 1H, CH (th-4), **9a**), 7.13 (s, 1H, CH (th-4), **8a**), 7.66 (s, 1H, CH (Py-3), **8a**), 8.08 (s, 1H, CH (Py-4), **9a**). ^{13}C NMR (75.47 MHz, $CDCl_3$, 24°C), δ: −1.34 ($Si(CH_3)_3$, **9a**), 1.45 ($Si(CH_3)_3$, **8a**), 15.02 (5−C−$\underline{CH_3}$, **9a**), 15.16 (5−C−$\underline{CH_3}$, **8a**), 24.92 (5−$\underline{CH_2}$−C, **9a**), 25.17 (5−$\underline{CH_2}$−C, **8a**), 117.23, 118.06 (CH (th-4), **8a**), 118.24, 127.38, 128.47 (CH (Py-3), **8a**), 135.68, 139.88, 145.00, 154.52 (C (th-5), **8a**), 160.90 (C (th-2), **9a**). MS (70 eV), *m/z*: 260 $[M]^+$, 245 $[M-CH_3]^+$, 243 $[M-2CH_3]^+$, 215 $[M-3CH_3]^+$, 200 $[M-4CH_3]^+$, 189 $[M-3CH_3-CN]^+$, 176 $[M- C_2H_4-2CH_3-CN]^+$. Analysis for $C_{13}H_{16}N_2SSi$ (260.44): Calcd.: C, 59.95; H, 6.19; N, 10.76; S, 12.31%. Found: C, 59.94; H, 6.22; N, 10.75; S, 12.25%.

2-Cyano-4-(trimethylsilyl)-5,6,7,8-tetrahydro[1]benzothieno[2,3-b]pyridine (8b) and 2-cyano-3-(trimethylsilyl)- 5,6,7,8-tetrahydro[1]benzothieno[2,3-b]pyridine (9b). The yield was 0.112 g (**8b**:**9b** = 1:3.2) (91%); white solid. ^1H NMR (300.13 MHz, $CDCl_3$, 24°C), δ: 0.50 (s, 9H, $Si(CH_3)_3$, **8b** and **9b**), 1.96 (s, 4H, $-C-\underline{CH_2}-\underline{CH_2}-C-$ (CHex), **8b** and **9b**), 2.71–3.05 (m, 4H, $-\underline{CH_2}-C-C-\underline{CH_2}-$ (CHex), **8b** and **9b**), 7.74 (s, 1H, CH (Py-3), **8b**), 7.94 (s, 1H, CH (Py-4), **9b**). ^{13}C NMR (75.47 MHz, $CDCl_3$, 24°C), δ: −1.32 ($Si(CH_3)_3$, **9b**), 1.67 ($Si(CH_3)_3$, **8b**), 22.00, 22.61 (5−C−$\underline{CH_2}$−C−C−4, **8b** and **9b**), 22.78, 22.89 (5−C−C−$\underline{CH_2}$−C−4, **8b** and **9b**), 23.18, 26.09 (5−$\underline{CH_2}$−C−C−C−4, **8b** and **9b**), 26.71, 26.85 (4−$\underline{CH_2}$−C−C−C−5, **8b** and **9b**), 118.36 (CN, **9b**), 118.93 (CN, **8b**), 126.88, 127.55 (CH (Py-3), **8b**), 129.39, 129.62, 132.35, 133.21 (CH (Py-4), **9b**), 133.96, 134.81, 139.81, 142.86, 143.61, 144.01, 160.96 (C (th-2), **9b**), 161.54 (C (th-2), **8b**). MS (70 eV), *m/z*: 286 $[M]^+$, 271 $[M-CH_3]^+$, 258 $[M-C_2H_4]^+$, 243 $[M-C_2H_4-CH_3]^+$, 228 $[M-C_2H_4-2CH_3]^+$, 228 $[M-C_2H_4-2CH_3-CN]^+$, 187 $[M-C_2H_4-3CH_3-CN]^+$, 174 $[M-2C_2H_4-2CH_3-CN]^+$. Analysis for $C_{15}H_{18}N_2SSi$ (286.48): Calcd.: C, 62.89; H, 6.33; N, 9.78; S, 11.19%. Found: C, 62.85; H, 6.32; N, 9.75; S, 11.10%.

6-Cyano-2-ethyl-4-(tributylstannyl)thieno[2,3-b]pyridine (10a) and 6-cyano-2-ethyl-5-(tributylstannyl)thieno[2,3-b]pyridine (11a). The yield was 0.204 g (**10a**:**11a** = 1:1.8) (88%); white solid. ^1H NMR (300.13 MHz, $CDCl_3$, 24°C),

δ: 0.87–0.95 (m, 6H, Sn−($\underline{CH_2}$−C−C−CH_3)$_3$, **10a** and **11a**), 1.20–1.70 (m, 24H, 5−C−$\underline{CH_3}$ + Sn−(C−$\underline{CH_2}$−$\underline{CH_2}$−$\underline{CH_3}$)$_3$, **10a** and **11a**), 2.99 (q, 2H, 5−$\underline{CH_2}$−CH_3 **10a** and **11a**), 6.91 (s, 1H, CH (th-4), **10a**), 6.98 (s, 1H, CH (th-4), **11a**), 7.66 (s, 1H, CH (Py-3), **10a**), 8.03 (s, 1H, CH (Py-4), **11a**). ^{13}C NMR (75.47 MHz, J modulation, $CDCl_3$, 24°C), δ: 10.12 (Sn(CH_2–)$_3$, **10a**), 10.42 (Sn(CH_2–)$_3$, **11a**), 13.60 (Sn−(C−C−C−$\underline{CH_3}$)$_3$, **10a** and **11a**), 14.91 (5−C−$\underline{CH_3}$, **10a** and **11a**), 17.53, 24.86, 26.84, 27.23, 27.84, 28.96, 116.85 (CH (th-4), **11a**), 118.27, 119.24 (CH (th-4), **10a**), 121.31, 126.83, 128.81, 131.15 (CH (Py-3), **10a**), 134.35, 135.80, 136.78, 137.67 (CH (Py-4), **11a**), 142.91, 150.32, 153.25, 153.67, 159.61 (C (th-2), **11a**). MS (70 eV), *m/z*: 478 $[M+1]^+$, 449 $[M-C_2H_4]^+$, 421 $[M-2C_2H_4]^+$, 365 $[M-2C_3H_6-C_2H_4]^+$, 307 $[M-CH_3 -3C_3H_7-CN]^+$, 146 $[M-Bu_3Sn-CN-CH_3]^+$. Analysis for $C_{22}H_{34}N_2SSn$ (477.30): Calcd.: C, 55.36; H, 7.18; N, 5.87; S, 6.72%. Found: C, 55.40; H, 7.21; N, 5.89; S, 6.61%.

2-Cyano-4-(tributylstannyl)-5,6,7,8-tetrahydro[1]benzothieno[2,3-b]pyridine (10b) and 2-cyano-3-(tributylstannyl)- 5,6,7,8-tetrahydro[1]benzothieno[2,3-b]pyridine (11b). The yield was 0.195 g (**10b**:**11b** = 1:8.3) (90%); white solid. ^{1}H NMR (300.13 MHz, $CDCl_3$, 24°C), δ: 0.87–0.97 (m, 6H, Sn−($\underline{CH_2}$−C−C−CH_3)$_3$, **10b** and **11b**), 1.30–1.73 (m, 21H, Sn−(C−$\underline{CH_2}$−$\underline{CH_2}$−$\underline{CH_3}$)$_3$, **10b** and **11b**), 1.96 (s, 4H, C−$\underline{CH_2}$−$\underline{CH_2}$−C (CHex), **10b** and **11b**), 2.75−2.92 (m, 4H, $\underline{CH_2}$−C−C−$\underline{CH_2}$ (CHex), **10b** and **11b**), 7.67 (s, 1H, CH (Py-3), **10b**), 7.90 (s, 1H, CH (Py-4), **11b**). MS (70 eV), *m/z*: 503 $[M]^{+\cdot}$475 $[M-C_2H_4]^+$, 446 $[M-2C_2H_4]^+$, 391 $[M-2C_3H_6-C_2H_4]^+$, 319 $[M-CH_3 -3C_3H_7-CN]^+$, 159 $[M-Bu_3Sn-CN-CH_3]^+$. Analysis for $C_{24}H_{36}N_2SSn$ (503.33): Calcd.: C, 57.27; H, 7.21; N, 5.57; S, 6.37%. Found: C, 57.25; H, 7.22; N, 5.62; S, 6.21%.

General Procedure for the Synthesis of Compounds 12–13a,b

A solution of propylamine or isopropylamine (0.029 g, 0.486 mmol) in toluene (1 mL) was added with stirring to a solution of compound **4a** (0.100 g, 0.486 mmol) in anhydrous toluene (2 mL). The reaction mixture was stirred at room temperature for 30 min and then refluxed for 2 h. Then the solvent was distilled off on a rotary evaporator, and the residue was purified by preparative thin-layer chromatography (silica gel; petroleum ether:EtOAc, 4:1 as the eluent).

2-Cyano-6-ethyl-3-propylthieno[2,3-d]pyrimidin-4-one (12a). The yield was 0.102 g (85%); white solid; mp 67°C. ^{1}H NMR (300.13 MHz, $CDCl_3$, 24°C), δ: 1.06 (t, 3H, −C−C−$\underline{CH_3}$), 1.38 (t, 3H, −C−$\underline{CH_3}$), 1.88 (sext, 2H, −C−$\underline{CH_2}$−CH_3), 2.94 (q, 2H, −$\underline{CH_2}$−CH_3), 4.27 (t, 2H, N−$\underline{CH_2}$−C−CH_3), 7.24 (s, 1H, CH (th-4)). ^{13}C NMR (75.47 MHz, $CDCl_3$, 24°C), δ: 11.04 (−C−C−$\underline{CH_3}$), 15.14 (5−C−CH_3), 22.61 (−C−$\underline{CH_2}$−CH_3), 24.26 (5−$\underline{CH_2}$−CH_3), 48.05 (−N−$\underline{CH_2}$−C−CH_3), 111.67 (CN), 118.47 (CH (th-4)), 127.34 (C (th-5)), 129.88 (C (th-3)), 151.27 ($\underline{C}$−CN), 155.88 (C (th-2)), 159.53 (−$\underline{C}$(O)−N−). MS (70 eV), *m/z*: 247 $[M]^+$, 232 $[M-CH_3]^+$, 221 $[M-CN]^+$, 205 $[M-CH_3 - CN]^+$, 190 $[M-2CH_3 - CN]^+$. Analysis for $C_{12}H_{13}N_3OS$ (247.32): Calcd.: C, 58.28; H, 5.30; N, 16.99; S, 12.97%. Found: C, 58.30; H, 5.23; N, 16.92; S, 12.90.

6-Ethyl-2-(propylamino)thieno[2,3-d]-1,3-oxazin-4-one (13a). The yield was 0.012 g (10%); white solid; mp 181°C. ^{1}H NMR (300.13 MHz, $CDCl_3$, 24°C), δ: 1.00 (t, 3H, −C−C−$\underline{CH_3}$), 1.31 (t, 3H, −C−$\underline{CH_3}$), 1.67 (sext, 2H, −C−$\underline{CH_2}$−CH_3), 2.76 (q, 2H, −$\underline{CH_2}$−CH_3), 3.38 (t, 2H, N−$\underline{CH_2}$−C−CH_3), 5.18 (s, 1H, NH), 6.87 (s, 1H, CH (th-4)). MS (70 eV), *m/z*: 238 $[M]^+$, 223 $[M-CH_3]^+$, 210 $[M-C_2H_4]^+$, 196 $[M-C_3H_6]^+$,

180 [M−C_3H_7NH]$^+$, 153 [M−C_3H_6−CH_3−CO]$^+$, 138 [M−C_3H_6−C_2H_5−CO]$^+$. Analysis for $C_{11}H_{14}N_2O_2S$ (238.31): Calcd.: C, 55.44; H, 5.92; N, 11.76%. Found: C, 55.39; H, 5.90; N, 11.79%.

6-Ethyl-2-(isopropylamino)thieno[2,3-d]-1,3-oxazin-4-one (13b). The yield was 0.092 g (80%); white solid; mp 172°C. ^{1}H NMR (300.13 MHz, $CDCl_3$, 24°C), δ: 1.20–1.30 (m, 9H, −C(CH$_3$)$_2$ and −C−CH$_3$), 2.75 (q, 2H, −CH$_2$−CH$_3$), 4.08 (sext, 1H, −CH(CH$_3$)$_2$), 5.28 (s, 1H, NH), 6.84 (s, 1H, CH (th-4)). ^{13}C NMR (75.47 MHz, $CDCl_3$, 24°C), δ: 15.20 (5−C−CH$_3$), 22.62 (−C(CH$_3$)$_2$), 23.62 (5−CH$_2$−CH$_3$), 43.94 (−N−CH(CH$_3$)$_2$), 110.39 (C (th-3)), 117.06 (CH (th-4)), 138.99 (C (th-5)), 155.13 (=N−C−NH), 155.35 (−C(O)−O−), 168.87 (C (th-2)). MS (70 eV), *m/z*: 238 [M]$^+$, 223 [M−CH_3]$^+$, 196 [M−C_3H_6]$^+$, 180 [M−C_3H_7NH]$^+$, 153 [M−C_3H_6 −CH_3−CO]$^+$, 138 [M−C_3H_6 −C_2H_5−CO]$^+$. Analysis for $C_{11}H_{14}N_2O_2S$ (238.31): Calcd.: C, 55.44; H, 5.92; N, 11.76%. Found: C, 55.39; H, 5.90; N, 11.79%.

General Procedure for the Synthesis of Compounds 14–15

A solution of propylamine or isopropylamine (0.058 g, 0.972 mmol) in toluene (1 mL) was added with stirring to a solution of compound **4a** (0.100 g, 0.486 mmol) in anhydrous toluene (4 mL). The reaction mixture was stirred at room temperature for 30 min and then refluxed for 2 h. The solvent was distilled off on a rotary evaporator, and the residue was purified by preparative thin-layer chromatography (silica gel; petroleum ether:EtOAc, 2:1 as the eluent).

[N-(3-Carboxy-5-ethylthienyl-2)]-N′,N″-bis(propyl)guanidine (14). The yield was 0.101 g (70%); white solid; mp 131°C. ^{1}H NMR (300.13 MHz, $CDCl_3$, 24°C), δ: 0.90–0.97 (m, 6H, N−C−C−CH$_3$), 1.25 (t, 3H, −C−CH$_3$), 1.52–1.63 (m, 4H, N−C−CH$_2$−CH$_3$), 2.68 (q, 2H, −CH$_2$−CH$_3$), 3.27 (m, 4H, N−CH$_2$−C−CH$_3$), 5.31 (s, 1H, NH−C_3H_7), 5.96 (s, 1H, NH−C(=NC_3H_7)−NHC_3H_7), 6.53 (s, 1H, CH (th-4)), 11.10 (s, 1H, COOH). ^{13}C NMR (75.47 MHz, $CDCl_3$, 24°C), δ: 11.27 (=N−C−C−CH$_3$), 11.41 (−HN−C−C−CH$_3$), 15.56 (5−C−CH_3), 22.92 (5−CH$_2$−CH_3), 23.01 (=N−C−CH$_2$−CH_3), 23.20 (−HN−C−CH$_2$−CH_3), 41.11 (=N−CH$_2$−C−CH_3), 42.45 (−HN−CH$_2$−C−CH_3), 111.03 (C−COOH (th-3)), 115.72 (CH (th-4)), 135.75 (C (th-5)), 148.13 (C−NH (th-2)), 154.07 (COOH), 165.92 (−NH−C(=N)−NH−). MS (70 eV), *m/z*: 297 [M]$^+$, 254 [M−C_3H_7]$^+$, 238 [M−C_2H_5−2CH_3]$^+$, 224 [M−2C_2H_5 −CH_3]$^+$, 212 [M−2C_3H_7]$^+$, 197 [M−2C_3H_7−CH_3]$^+$, 180 [M−2C_3H_7 −CH_3−OH]$^+$, 153 [M−$C_7H_{15}N_2$−OH]$^+$, 138 [M−$C_7H_{15}N_2$−OH−CH_3]$^+$. Analysis for $C_{14}H_{23}N_3O_2S$ (297.42): Calcd.: C, 56.54; H, 7.79; N, 14.13; S, 10.78%. Found: C, 56.50; H, 7.72; N, 14.12; S, 10.56%.

[N-(3-Carboxy-5-ethylthienyl-2)]-N′,N″-bis(isopropyl)guanidine (15). The yield was 0.107 g (74%); white solid; mp 127–128°C. ^{1}H NMR (300.13 MHz, $CDCl_3$, 24°C), δ: 1.15–1.25 (m, 15H, −C(CH$_3$)$_2$ and −C−CH$_3$), 2.67 (q, 2H, −CH$_2$−CH$_3$), 3.93 (sext, 1H, −HN−CH(CH$_3$)$_2$), 4.18 (sext, 1H, =N−CH(CH$_3$)$_2$), 5.02 (s, 1H, $^3J_{HH}$ = 7.36 Hz, −NH−CH(CH$_3$)$_2$), 5.78 (s, 1H, $^3J_{HH}$ = 7.36 Hz, −NH−C(=N)−NHC_3H_7−*i*), 6.54 (s, 1H, CH (th-4)), 11.06 (s, 1H, COOH). ^{13}C NMR (75.47 MHz, $CDCl_3$, 24°C), δ: 15.58 (5−C−CH$_3$), 22.83 (−NH−C(CH$_3$)$_2$), 22.88 (5−CH$_2$−CH_3), 23.08 (=N−C(CH$_3$)$_2$), 41.25 (−HN−CH(CH$_3$)$_2$), 42.56 (=N−CH(CH$_3$)$_2$), 110.91 (C−COOH (th-3)), 115.76 (CH (th-4)), 135.44 (C (th-5)), 147.93 (C-NH (th-2)), 153.11 (COOH), 164.99 (−NH−C(=N)−NH−). MS (70 eV), *m/z*: 297 [M]$^+$, 279 [M−H_2O]$^+$, 253

$[M-C_2H_5\ -CH_3]^+$, 237 $[M-4CH_3]^+$, 224 $[M-C_3H_7-2CH_3]^+$, 212 $[M-2C_3H_7]^+$, 197 $[M-2C_3H_7-CH_3]^+$, 180 $[M-2C_3H_7-CH_3-OH]^+$, 153 $[M-C_7H_{15}N_2-OH]^+$, 138 $[M-C_7H_{15}N_2-OH-CH_3]^+$. Analysis for $C_{14}H_{23}N_3O_2S$ (297.42): Calcd.: C, 56.54; H, 7.79; N, 14.13; S, 10.78%. Found: C, 56.50; H, 7.72; N, 14.12; S, 10.56%.

REFERENCES

1. (a) K. Kim, *Sulfur Reports*, **21,** 147 (1998) (b) L. S. Konstantinova and O. A. Rakitin, *Uspekhi Khimii (Russian Chemical Reviews)*, **77,** 551 (2008).
2. P. G. Baraldi, M. G. Pavani, M. C. Nuñez, P. Brigidi, B. Vitali, R. Gambari, and R. Romagnoli, *Bioorg. Med. Chem.*, **10,** 449 (2002).
3. V. Thiery, T. Besson, and C. W. Rees, *Synthesis*, 1345 (1999).
4. V. N. Yarovenko, A. A. Es'kov, G. V. Zatonsky, I. V. Zavarzin, M. M. Krayushkin, B. B. Averkiev, and M. Yu. Antipin, *J. Heterocycl. Chem.*, **41,** 37 (2004).
5. V. N. Yarovenko, A. A. Eskov, P. A. Kondrashev, A. V. Ignatenko, I. V. Zavarzin, L. G. Vorontsova, I. P. Sedishev, M. M. Krayushkin, and Z. A. Starikova, *Heterocycles*, **65,** 1601 (2005).
6. (a) H.-S. Lee, Y.-G. Chang, and K. Kim, *J. Heterocycl. Chem.*, **35,** 659 (1998) (b) P. K. Mohanta, and K. A. Kim, *Tetrahedron Lett.*, **43,** 3993 (2002).
7. (a) M. de F. Pereira, V. Thiery, and T. Besson, *J. Sulf. Chem.*, **27,** 49 (2006); (b) P. K. Mohanta, and K. Kim, *Heterocycles*, **57,** 1471 (2002); (c) P. K. Mohanta and K. Kim, *Tetrahedron Lett.*, **43,** 3993 (2002); (d) Y.-G. Chang and K. Kim, *Heterocycles*, **51,** 2653 (1999); (e) C. Cristoborou, P. A. Koutentis, and S. S. Michaelidou, *Arkivoc*, **2006,** 207 (2007); (f) H. Rouillard, P. Pineau, L. Domon, and V. Thiery, *23 Int. Sym. Org. Chem. Sulf. (ISOCS-23)*, Moscow, Russia, *Book of Abst.*, 132 (2008).
8. (a) V. N. Charushin, N. N. Mochulskaya, A. A. Andreiko, M. I. Kodess, and O. N. Chupakhin, *Mendeleev Commun.*, **2002**, 28 (2002); (b) V. P. Litvinov, V. V. Dotsenko, and S. G. Krivokolysko, In *Chemistry of Thienopyridines and Related Systems,* [in Russian] L. I. Belen'kii, Ed., (Nauka, Moscow, 2006), 407 pp.
9. T. Besson, K. Emayan, and C. W. Rees, *J. Chem. Soc., Perkin Trans. 1*, 2097 (1995).
10. H. Lee and K. Kim, *Heteroatom Chem.*, **4,** 263 (1993).
11. (a) C. W. Rees, *J. Heterocycl. Chem.*, **29,** 639 (1992); (b) M.-K. Jeon, K. Kim, and Y. J. Park, *Chem. Commun.*, 1412 (2001).
12. K. Matsumoto, A. Sera, and H. Katsura, *Heterocycles*, **47,** 1135 (1998).
13. M. M. Krayushkin, V. N. Yarovenko, I. P. Sedishev, A. A. Andreyko, N. N. Mochulskaya, and V. N. Charushin, *Mendeleev Commun.*, **2005**, 151 (2005).
14. H. Lee, K. Kim, and D. Whang, *J. Org. Chem.*, **59,** 6179 (1994).
15. G. I. Nikishin, S. S. Spektor, G. P. Shakhovskoi, V. G. Glukhovtsev, and V. M. Zhulin, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1664 (1976) [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, **1976** (Engl. Transl.)].
16. K. Gewald, E. Schrinke, and H. Bottcher, *Chem. Ber.*, **99,** 94 (1966).
17. R. Appel, H. Janssen, M. Siray, and F. Knoch, *Chem. Ber.*, **118,** 1632 (1985).