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Reactions and Reactivity of Thienopyridines: Facile Synthesis of Some Pyridothienooxazepine Derivatives

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Pyridothienooxazepines were synthesized by the interaction salt of the 3-aminothienopyridine-2-carboxylate with activated α-haloketones or α-halonitriles. Several derivatives of thienopyridine were prepared either by the replacement of an amino group or by using an amino group in 3-aminothienopyridine-2-carboxylate to synthesize another derivative of thienopyridine.

Keywords Reactions; synthesis; thienopyridines; triazolylthienopyridine; thienopyridoxazepines

INTRODUCTION

Oxazepines have attracted widespread interest in view of their biological and pharmacological activities.[1] Oxazepines and benzoxazepines have been the subject of the most extensive studies, and numerous synthetic methods have been developed for them.[2–5] Compared to the heterocyclic system fused with oxazepines, the articles that describe the synthesis of a heterocyclic system fused with oxazepines are limited,[6–9] and there is no one article reported that describes the synthesis of pyridothienoxazepines.

Many thienopyridines have been evaluated pharmacologically and have been found to show activity against, for example, diabetes mellitus,[10–12] and as analgesics and antiinflammatories, sedatives,[13] anticoagulants,[14] antiartherosclerotics,[15] and gonadotropin-releasing hormone antagonists.[16] In continuation of our program in the synthesis of heterocycles compounds containing a thieno[2,3-b] pyridine moiety,[17–25] we report herein the synthesis of some new thienopyridine derivatives with hope that they have potential biological activities.

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RESULTS AND DISCUSSIONS

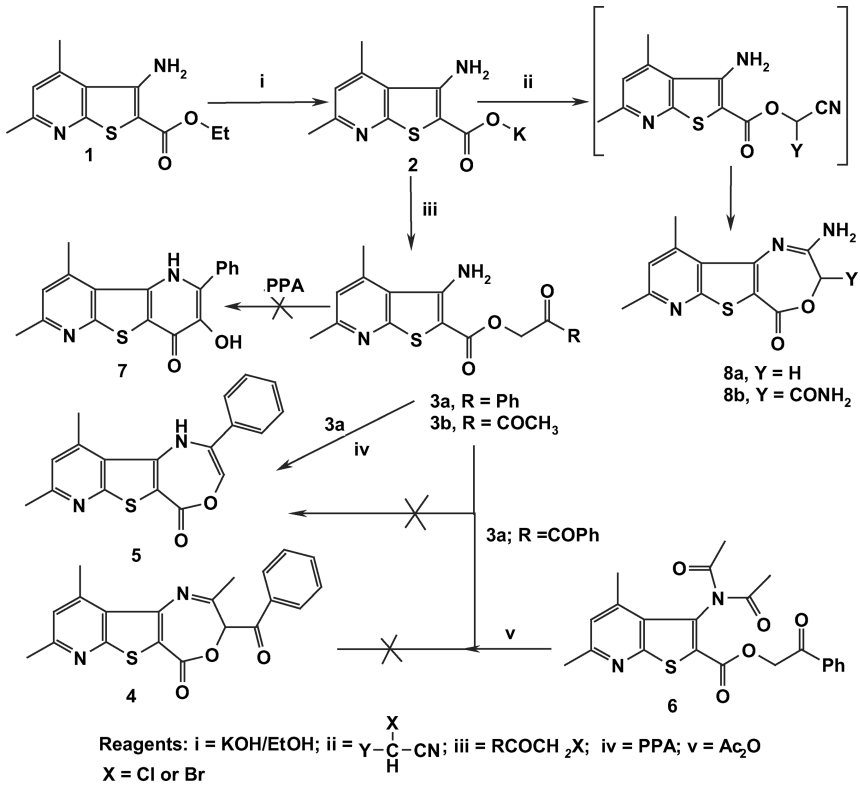
The potassium salt of 3-aminothieno[2,3-b]pyridine-2-carboxylate **2** was reacted with phenacyl bromide and/or chloroacetone to afford the corresponding esters **3a,b**. In an attempt to cyclize the produced compound **3a** with acetic anhydride, neither compounds **4** nor **5** were obtained, but diacylation of an amino group occurred to give diacylated amino derivative **6**. The formation of compound **6** was established on the basis of NMR and mass spectra of the produced compound. The NMR spectrum revealed two signals at δ 2.2 and 2.3 corresponding to the two acetyl groups. The mass spectrum gave a molecular ion beak at 424 corresponding to the molecular weight of **6**.

The synthesis of compound **5** was accomplished according to the literature, [26,27] which used a phenacyl ester of anthranilic acid. Similarly, when ester **3a** was treated with polyphosphoric acid expecting that the rearrangement accompanied with cyclization occurred to give pyridinothienopyridone derivative **7**, but in our case the dedydration occurred to give oxazepine **5**. The structure was established on the basis of ^{1}H NMR, while its spectrum revealed signals at δ 6.95 for the -CH- pyridine and at d 7.15 for the –CH- of oxzazepine.

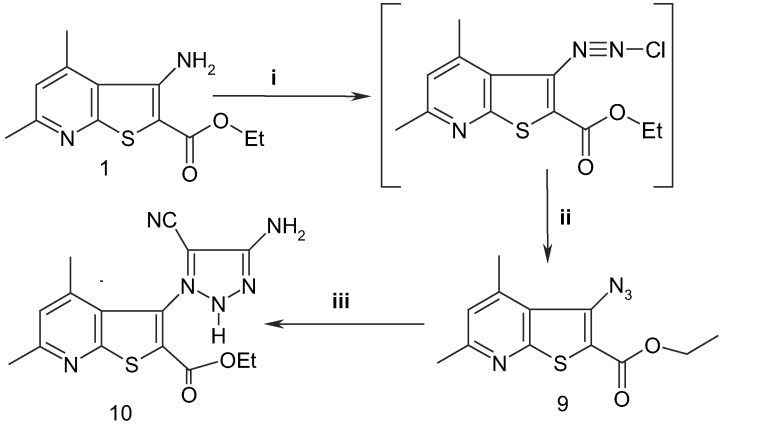
On the other hand, when salt **2** was allowed to react with α-halogenated nitrile, namely chloroacetonitrile and α-bromcyanoacetamide, the corresponding ester was formed as an intermediate, which spontaneously cyclized under the reaction condition to give the oxazepine **8a,b** (Scheme 1). The structure of oxazepine was confirmed using IR, ^{1}H NMR, and mass spectra, while the IR did not reveal any absorption band for the CN group and at the same time gave a band at 3350 and 3250 characteristic for the amino group. Also the mass spectrum gave a peak at 260 as a molecular ion peak. The ^{1}H NMR of compound **8** in ($CDCl_3$) gave a characteristic signal at δ 4.85 characteristic for -CH_2- and at δ −6.3 for NH_2; the latter signal disappeared when treated with D_2O.

The amino group in ethyl 3-aminothienopyridine-2-carboxylate **1** was converted into the corresponding diazonium chloride upon treatment with sodium nitrite in the presence of HCl. The produced diazonium chloride underwent a Sandmeyer reaction, which was replaced with the azido group when treated with sodium azide in situ to give the corresponding azido derivative **9**. The azido group underwent cycloaddition reaction with malononitrile to afford the triazolyl derivative **10** (Scheme 2).

When 3-amino-4,6-dimethylthieno[2,3-b]pyridine **11a** and 3-amino-2,4,6-trimethylthieno[2,3-b] pyridine **11b** were allowed to react with chloroacetyl chloride in dioxane followed by treating with sod, carbonate



SCHEME 1



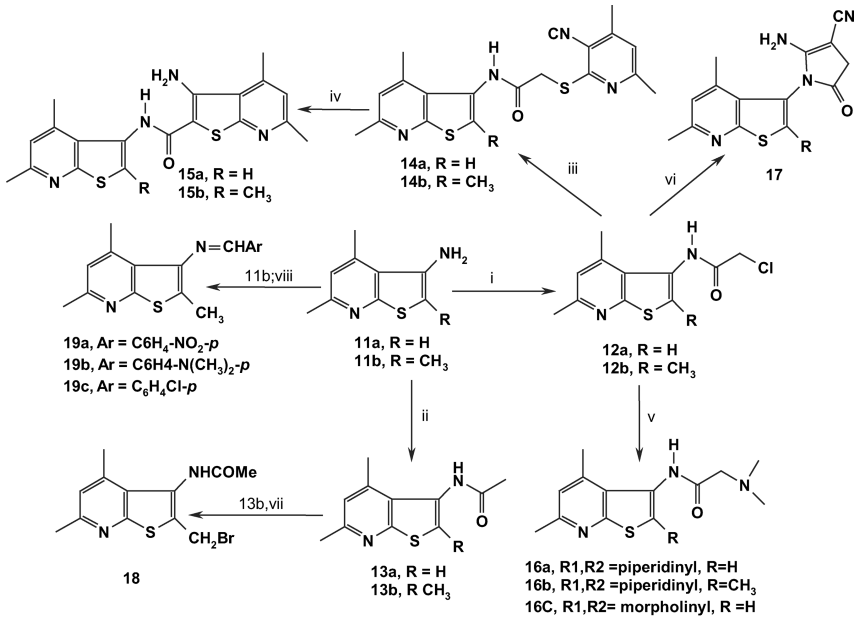
SCHEME 2

afforded the corresponding chloroacetylamino derivative **12a,b**, but when they were allowed to react with acetic anhydride on a steam bath at 60°C, they afforded N-acyl derivatives **13a,b**.

Chloroacetyl compounds **21a,b** were reacted with 4,6-dimethyl-2-mercapto-pyridine-3-carbonitrile in ethanol and in the presence of sodium acetate to afford pyridylmercaptoacetaminothienopyridine derivatives **14a,b**, which, upon treatment with sod, ethoxide in ethanol, were cyclized into thienopyridinoylaminothienopyridines **15a,b**. Also, the chloroacetyl derivatives **12a,b** were condensed with secondary amines to afforded compounds **16a,b**. The reaction of chloroacetyl derivative **12** with malononitrile in ethanol in the presence of sodium ethoxide afford the pyrrolyl derivative **17**. Bromination of acyl compound **13b** using bromine/acetic at r.t. afforded 2-bromomethylthienopyridine derivative **18**. The condensation of amino compounds **11b** with aromatic aldehyde gave the corresponding Schiff's base **19** (Scheme 3).

EXPERIMENTAL

All melting points were uncorrected and were determined on a Kofler melting-point apparatus. IR spectra were recorded on a Pye-Unicam



Reagents: i =$ClCH_2COCl$/dioxan; ii= Ac_2O; iii =4,6-dimethyl-2-mercapropyridine-3-carbonitrile/EtOH/AcONa; iv = EtOH/EtONa; v = R_1R_2NH; vi = EtOH/EtONa; vii = Br_2/AcOH; viii = ArCHO/EtOH

SCHEME 3

spectrometer using the KBr Wafer technique. ^{1}H NMR spectra were recorded on a Varian 390 90 MHz and JEOL 400 MHz NMR spectrometers using TMS as an internal standard. Chemical shifts were expressed as δ, units ppm. Mass spectra were recorded in on JEOL JMS 600 spectrometer. Elemental analyses were performed on a Perkin-Elmer 240 C.

The Synthesis of 3a,b and 8ab:General Procedure

To a stirred suspension of potassium salt **1** (1.3 g, 5 mmol) in DMF (30 mL), α-halocompound (0.005 mol), namely phenacyl bromide, chloroacetone, chloroacetonitrile or α-bromocyanoacetamide, was added. The reaction mixture was stirred at r.t. (30°C) for 2 h and then poured to an ice/water mixture (200 g). The solid product was collected and recrystallized from ethanol.

Benzoylmethyl 3-aminothieno[2,3-b]pyridine-2-carboxylate (3a)

Produced as white crystals, 1.5 g (88%), m.p. 210°C. IR: $\nu = 3410$, 3310 cm^{-1} (NH_2), 1680 cm^{-1} (C=O). ^{1}H NMR($CDCl_3$): 2.5, 2.8 (2s, 6H, $3CH_3$), 5.5 (s, 2H, CH_2), 6.4 (s, 2H, NH_2), 6.85 (s, 1H, CH-pyridine) and 7.2–8.0 (m,5H, Ar-H).

Anal. calcd. for $C_{18}H_{16}N_2O_3S$(340.40): C, 63.51; H, 4.74; N, 8.23; S, 9.42%. Found: C, 63.69; H, 4.53; N, 8.00; S, 9.18%.

Acetylmethyl 3-aminothieno [2,3-b]pyridine-2-carboxylate (3b)

Produced as white crystals, 1.14 g (82%) yield, m.p. 160°C. IR: $\nu = 3400$, 3300 cm^{-1} (NH_2), 1680 cm^{-1} (C=O). ^{1}H NMR ($CDCl_3$): 2.2, 2.4, 2.6 (3s, 9H, $3CH_3$), 4.7 (s, 2H, CH_2), 6.15, (s, 2H, NH_2) and 6.85 (s, 1H, CH-pyridine).

Anal. calcd. for $C_{13}H_{14}N_2O_3S$ (278.33): C, 56.10; H, 5.07; N, 10.06; S, 11.52%. Found: C, 55.92; H, 5.34; N, 10.17; S, 11.29%.

2-Amino-8,10-dimethyl-3[H]-pyrido[2′,3′:2,3]thieno[4,5-e][1,4] Oxazepin-5-one (8a)

Produced as white crystals, 1.07 g (85%), m.p. 238°C. IR: $\nu =$ 3350, 3250 cm^{-1} (NH_2), 1695 cm^{-1} (C=O). ^{1}H NMR($CDCl_3$): 2.6, 2.75(2s. 6H, $2CH_3$), 4.85(s, 2H, CH_2), 6.3(s, 2H, NH_2) and at 6.9(s, 1H, CH-pyridine). MS: M^+(260) as a molecular ion peak and base peak (203, 175, 148, 131, 103, 76, 39).

Anal. calcd. for $C_{12}H_{11}N_3O_2S$ (261.30): C, 55.16; H, 4.24; N, 16.08; S, 12.27%. Found: C, 54.92; H, 4.08; N, 15.90; S, 12.52%.

2-Amino-8,10-dimethyl-3[H]-5-oxo-pyrido[2′,3′:2,3]thieno[4,5-e][1,4]oxazepin-3-carboxamide (8b)

Produced as yellow crystals 1.34 g (68%), m.p. 285°C. IR: $\nu = 3350$, 3250 cm^{-1} (NH_2), 1695 cm^{-1} (C=O). ^1H NMR($CDCl_3$): 2.6, 2.85 (2s, 6H, $2CH_3$), 5.2(s, 1H, CH), 6.3 (s, 2H, NH_2), 6.9 (s, 1H, CH-pyridine) and 7.8 (s, 2H, $CONH_2$).

Anal. calcd. for $C_{13}H_{12}N_4O_3S$ (304.33): C, 51.31; H, 3.97; N, 18.41; S, 10.54%. Found: C, 51.52; H, 4.17; N, 18.63; S, 10.52%.

Benzoylmethyl 3-diacetylaminothieno[2,3-b]pyridine-2-carboxylate 6

A sample of compound **3a** (1.7 g, 5 mmol) in acetic anhydride (10 mL) was heated under reflux for 4 h, allowed to cool, and poured into cold water (500 mL). The solid product was collected and recrystallized from ethanol as white crystals, 1.74 g (82%), m.p. 187–188°C. IR: $\nu = 173$, 1720, 1700 cm^{-1} (3CO). ^1H NMR($CDCl_3$): $\delta = 2.2$, 2.3, 2.7, 2.9 (4s, 12H, $4CH_3$), 5.6 (s, 2H, CH_2), 6.9 (s, 1H, CH-pyridine), 7.1–7.7 (m, 5H, Ar-H). MS: M^+(424) as a molecular ion peak.

Anal. calcd. for $C_{22}H_{20}N_2O_5S$ (424.48): C, 62.25; H, 4.75; N, 6.60; S, 7.55%. Found: C, 62.08; H, 4.94; N, 6.84; S, 7.29%.

8,10-Dimethyl-2-phenyl-1[H]-pyrido[2′,3′:2,3]thieno[4,5-e][1,4]oxazepin-5-one (5)

A sample of compound **3a** (1.7 g, 5 mmol) in polyphosphoric acid (10 mL) was heated at 60–70°C on a steam bath for 4 h, poured into cold water, and neutralized with ammonia solution. The solid product was collected and recrystallized from dioxan as white crystals 0.97 g (60%). IR: $\nu = 3270$ cm^{-1} (NH), 1690 cm^{-1} (CO). ^1H NMR(DMSO-d_6): 2.7, 3.0 (2s, 6H, $2CH_3$), 6.95 (s, 1H, CH-pyridine), 7.15 (s, 1H, CH-oxzaepine), 7.2–8.3 (m, 5H, Ar-H), 8.9 (s, 1H, NH).

Anal. calcd. for $C_{18}H_{14}N_2O_2S$ (322.39): C, 67.06; H, 4.38; N, 8.69; S, 9.95%. Found: C, 66.86; H, 4.568; N, 8.47; S, 10.21%.

Ethyl 3-Azido-4,6-dimethylthieno[2,3-b]pyridine-2-carboxylate (9)

To a stirred cooled solution at 0–5°C of compound **1** (2.5 g, 10 mmol) in an HCl/water mixture (2 mL conc. HCl, 5 mL, H_2O), sod. nitrite solution

(0.7 g in 3 mL H_2O) was added dropwise. After the addition was finished, stirring of the solution was continued for 30 min and then allowed to stand for 1 h. A solution of sodium azide (10 mmol in 2 mL H_2O) was added dropwise. The azido compound was collected by filtration, 1.77g (64%), m.p. 80°C decomposed and used without further purification. IR: $\nu = 2200$ cm^{-1} (N_3), 1700 cm^{-1} (CO). ^{1}H NMR ($CDCl_3$): 1.3 (t, 3H, CH_3 ester), 2.6, 2.9 (2s, 6H, $2CH_3$ pyridine), 4.0 (q, 2H, CH_2 ester) and 6.95 (s, 1H, CH-pyridine).

Anal. calcd. for $C_{12}H_{12}N_4O_2S$ (276.32): C, 52.16; H, 4.38; N, 20.28; S, 11.60%. Found: C, 52.03; H, 4.14; N, 20.51; S, 11.84%.

Ethyl 4,5-dimethyl-[4,amino-5-cyano-2(H)(1,2,3)triazol-1-yl)]thieno[2,3-b]pyridine-2-carboxylate (10)

A mixture of Azide compound **9** (1.38 g, 0.005 mol) and malononitrile (0.33 g, 5 mmol) in absolute ethanol (20 mL) containing sod. ethoxide (0.001 mol) was stirred at r.t. for 1 h, refluxed on a steam bath for an additional h, and then allowed to cool. The solid product was collected and recrystallized from ethanol as yellow crystals 1.1 g (64%) yield, m.p. 218°C. IR: $\nu = 3440$, 3340, 3210 cm^{-1}(NH_2, NH), 2950 cm^{-1}(CH aliphatic), 2220 cm^{-1}(CN) and at 1710 cm^{-1} (CO). ^{1}H NMR(DMSO-d_6): 1.3 (t, 3H, CH_3 ester), 2.6, 2.9 (2s, 6H, $2CH_3$ pyridine), 3.9(q, 2H, CH_2 ester), 6.4(s, 2H, NH_2) and 6.95 (s, 1H, CH-pyridine), 10.5 (NH).

Anal. calcd. for $C_{15}H_{16}N_6O_2S$(344.40): C, 52.31; H, 4.68; N, 24.40; S, 9.31%. Found: C, 52.14; H, 4.44; N, 24.63; S, 9.54%.

3-Amino-4,6-dimethylthieno[2,3-b]pyridine (11a)

This was prepared according to the literature.[28]

3-Amino-2,4,6-trimethylthieno[2,3-b]pyridine (11b)

This was prepared according to the literature.[17]

3-Chloroacetylamino-2-(H) or (CH_3)-4,6-trimethylthieno [2,3-b]pyridine(12a,b)

To a solution of compound **11a** and/or **11b** (0.01 mol) in dioxan (50 mL), chloroacetyl chloride (0.01 mol) was added dropwise with stirring and then heated on a steam bath at 50°C for 1h. The reaction micture was poured into cold water (400 mL) and neutralized with sod. carbonate solution 10%. The solid product was collected and dried.

12a; R = H; recrystallized from toluene as yellowish white crystals 1.99 g (78%), m.p. 180°C.

IR: $\nu = 3250$ cm^{-1}(NH), 1690 (C=O). ^{1}H NMR ($CDCl_3$): $\delta = 2.6$, 2.8 (2s. 6H, $2CH_3$), 4.25 (s, 2H, CH_2), 6.90(s, 1H, CH-thiophene), 7.1 (s, 1H, CH-pyridine), 8.95 (s, 1H, NH).

Anal. calcd. for $C_{11}H_{11}ClN_2OS$ (254.74): C, 51.86; H, 4.35; Cl, 13.92; N, 11.00; S, 12.59%. Found: C, 52.08; H, 4.12; Cl, 14.15; N, 10.82; S, 12.37%.

12b; R = CH_3; recrystallized from toluene as yellowish white crystals 1.99 g (74%), m.p. 217–218°C.

IR: $\nu = 3250$ cm^{-1}(NH), 1690 (C=O). ^{1}H NMR ($CDCl_3$): $\delta = 2.4$, 2.7, 2.9 (3s. 9H, $3CH_3$), 4.25 (s, 2H, CH_2), 6.9 (s, 1H, CH-pyridine), 9.95 (s, 1H, NH).

Anal. calcd. for $C_{12}H_{13}ClN_2OS$ (268.76): C, 53.63; H, 4.88; Cl, 13.19; N, 10.42; S, 11.93%. Found: C, 53.41; H, 5.06; Cl, 13.36; N, 10.63; S, 12.18%.

3-Aceylamino-4,6-dimethylthieno[2,3-b]pyridine or 3-Aceylamino-2,4,6-trimethylthieno[2,3-b] pyridine(13a,b)

A sample of compound **11** (0.005 mol) in acetic anhydride (20 mL) was heated at 60°C on a steam bath for 1 h, allowed to cool, poured into an ice/water mixture (200 g), and then neutralized with aq. ammonia until it became alkaline to litmus paper. The solid product was collected and recrystallized from ethanol as white crystals.

13a, the product is 1.43 g (65%), m.p. 205°C Lit.[28] m.p. 205°C.

13b, the product is 0.84 g (72%), m.p. 200°C.

Anal. calcd. for $C_{12}H_{14}N_2OS$ (234.32): C, 61.51; H, 6.02; N, 11.96; S, 13.68%. Found: C, 61.72; H, 5.79; N, 12.20; S, 13.81%.

IR: $\nu = 3250$ cm^{-1} (NH) and 1680 cm^{-1} (C=O). ^{1}H NMR ($CDCl_3$): 2.4, 2.7, 2.9 (3s, 9H, $3CH_3$), 7.0 (s, 1H, CH-pyridine) and 10.5 (s, 1H, NH).

Pyridylmercaptoacetylaminothienopyridine 14a,b

A mixture of compound **12** (0.005 mol), 2-mercaptopyridine-3-carbonitrile (0.01 mol), and sodium acetate (0.02 mol) in ethanol (50 mL) was heated under reflux for 3 h, allowed to cool, filtered off, washed well with water, and dried.

14a; R = H; the product was recrystallized from ethanol as white crystals 1.3 g (68%), m.p. 203°C.

IR: $\nu = 3260$ cm^{-1} (NH), 2220 cm^{-1} (CN), and 1690 cm^{-1} (CO). ^{1}H NMR ($CDCl_3$): $\delta = 2.6$, 2.8 (4s. 12H, $4CH_3$), 4.25 (s, 2H, CH_2), 6.9(s, 1H, CH-thiophene), 7.05 (s, 2H, 2CH-pyridine), 8.95 (s, 1H, NH).

Anal. calcd. for $C_{19}H_{18}N_4OS_2$ (382.51): C, 59.66; H, 4.74; N, 14.65; S, 16.77%. Found: C, 59.85; H, 4.98; N, 14.39; S, 17.00%.

14b; R = Me; the product was recrystallized from ethanol as yellowish white crystals 1.29 g (65%), m.p. 237–239°C.

IR: $\nu = 3310$ cm^{-1} (NH), 2220 cm^{-1} (CN), and 1690 cm^{-1} (CO). ^{1}H NMR ($CDCl_3$): $\delta = 2.3$, 2.6, 2.8 (5s, 15H, $5CH_3$), 4.25 (s, 2H, CH_2), 6.9 (s, 2H, 2CH-pyridine), 8.95 (s, 1H, NH).

Anal. calcd. for $C_{20}H_{20}N_4OS_2$ (396.54): C, 60.58; H, 5.08; N, 14.13; S, 16.17%. Found: C, 60.78; H, 4.88; N, 14.00; S, 16.38%.

3-Amino-4,6-dimethyl-2-N-[4,6-dimethylthieno[2,3-b]pyridine-3-yl]thieno[2,3-b]pyridinecarbo-xamide (15a) and 3-Amino-4,6-dimethyl-2-N-[2,4,6-trimethylthieno[2,3-b]pyridine-3-yl]-thieno[2,3-b]pyridine-carboxamide 15b

A sample of compound **14** (0.005 mol) in absolute ethanol (20 mL) containing [0.005 mol] sod. ethoxide was refluxed for 1 h, and then allowed to cool. The solid product was collected, washed with water, and recrystallized from dioxin.

15a, produced as white crystals 1.37 g (72), m.p. > 300°C.

IR: $\nu = 3450$, 3350, 3180 cm^{-1} (NH_2, NH) and 1670 cm^{-1} (CO). ^{1}H NMR (DMSO-d_6):$\delta = 2.6$, 2.8 (4s, 12H, $4CH_3$), 6.25 (s, 2H, NH_2), 6.75 (s, 1H, CH-thiophene), 6.9 (s, 2H, 2CH-pyridine), 8.95 (s, 1H, NH).

Anal. calcd. for $C_{19}H_{18}N_4OS_2$ (382.51): C, 59.66; H, 4.74; N, 14.65; S, 16.77%. Found: C, 59.42; H, 4.52; N, 14.90; S, 16.61%.

15b, produced as white crystals 1.27 g (64%), m.p. > 300°C.

IR: $\nu = 3400$, 3300, 3220 cm^{-1} (NH_2, NH) and 1670 cm^{-1} (CO). ^{1}H NMR (DMSO-d_6):$\delta = 2.3$, 2.6, 2.8 (5s, 15H, $5CH_3$), 6.3 (s, 2H, NH_2), 6.9 (s, 2H, 2CH-pyridine), 8.95 (s, 1H, NH).

Anal. calcd. for $C_{20}H_{20}N_4OS_2$ (396.54): C, 60.58; H, 5.08; N, 14.13; S, 16.17%. Found: C, 60.33; H, 5.30; N, 13.89; S, 15.95%.

3-Alkyl(aryl)aminoacetylamino-4,6-dimethylthieno[2,3-b]pyridine and 3-Alkyl(aryl)amino-2,4,6-trimethylthieno[2,3-b]pyridine(16a–c)

A mixture of compound **12** (0.005 mol) and alkyl amine or aryl amine (2 mol) was heated above their melting point for 30 min and then ethanol (30 mL) was added, and the reflux was continued for an additional hour. The solvent was evaporated under vacuum, and the residue was washed with sodium carbonate solution (50 mL, 10%). The solid product was collected and recrystallized from the proper solvent.

16a, R = H, R_1, R_2 = -$(CH_2)_5$-; produced 1.9 g (72), m.p. 195°C.

IR: $\nu = 3330$ cm^{-1} (NH), 1700 cm^{-1} (C=O). ^{1}H NMR($CDCl_3$): $\delta = 1.6$ (m, 9H, $3CH_2$), 1.8 (m, 4h, $2CH_2$), 2.6, 2.8 (2s, 6H, $2CH_3$), 3.95(s, 2H, CH_2), 6.9 (s, 1H, CH-pyridine), 8.0(s, 1H, CH-thiophene), 9.95 (s, 1H, NH).

Anal. calcd. for $C_{16}H_{21}N_3OS$(303.42): C, 63.33; H, 6.98; N, 13.85; S, 10.57%. Found: C, 63.17; H, 6.78; N, 14.08; S, 10.37%.

16b, R = CH_3, R_1, R_2 = -$(CH_2)_5$-; produced 1.1 g (70%), m.p. 133–135°C.

IR: $\nu = 3270$ cm^{-1} (NH), 1680 cm^{-1} (C=O). ^{1}H NMR($CDCl_3$: $\delta = 1.5$ (m, 9H, $3CH_2$), 2.3 (m, 4H, $2CH_2$), 2.2 (s, 3H, CH_3), 2.6, 2.9 (2s, 6H, $2CH_3$), 3.6(s, 2H, CH_2), 6.9 (s, 1H, CH-pyridine), 9.95 (s, 1H, NH).

Anal. calcd. for $C_{17}H_{23}N_3OS$(317.45): C, 64.32; H, 7.30; N, 13.24; S, 10.10%. Found: C, 64.08; H, 7.11; N, 13.43; S, 9.88%.

16c, , R = H, R_1, R_2 = -$(CH_2)_4O$-; produced 1.16 g (76), m.p. 193–195°C.

Anal. calcd. for $C_{15}H_{19}N_3O_2S$(305.40): C, 58.99; H, 6.27; N, 13.76; S, 10.50%. Found: C, 59.22; H, 6.03; N, 14.00; S, 10.37%.

IR: $\nu = 3250$ cm^{-1} (NH), 1690 cm^{-1} (C=O). ^{1}H NMR($CDCl_3$): $\delta = 2.7$ (m, 4H, $2CH_2$), 3.1 (m, 4H, $2CH_2$), 2.6, 2.9 (2s, 6H, $2CH_3$), 3.99(s, 2H, CH_2), 6.85(s, 1H, CH-thiophene), 6.95 (s, 1H, CH-pyridine), 9.95 (s, 1H, NH).

4,6-Dimethy-3-[2-amino-3-cyano-5-oxopyrrolidin-1-yl]thieno [2,3-b]pyridine(17a) and 2,4,6-Trimethyl-3-[2-amino-3-cyano-5-oxopyrrolidin-1-yl]thieno[2,3-b]pyridine(17b)

A mixture of compound **12** (0.005 mol) and malononitrile (0.33 g, 5 mmol) in ethanol (20 mL) containing sod. ethoxide (0.005 mol) was heated under reflux for 4 h, allowed to cool, and poured into water (100 mL). The solid product was collected and recrystallized from ethanol.

17a; produced 0.94 g (66%), m.p. 175°C.

IR: $\nu = 3360$, 3260 cm^{-1}(NH_2), 2220 cm^{-1} (CN), 1670 cm^{-1}(CO). ^{1}H NMR(DMSO-d_6): $\delta = 2.6$, 2.9 (2s, 6H, $2CH_3$), 3.8 (s, 2H, CH_2), 6.4 (s, 2H, NH_2), 6.9 (s, 1H, CH-thiophene), 7.0 (s, 1H, CH-pyridine).

Anal. calcd. for $C_{14}H_{12}N_4OS$(284.34): C, 59.14; H, 4.25; N, 19.70; S, 11.28%. Found: C, 58.90; H, 4.01; N, 19.93; S, 11.51%.

17b; produced 0.92 g (62%), m.p. > 300°C.

IR: $\nu = 3390$, 3290 cm^{-1} (NH_2), 2220 cm^{-1} (CN), 1670 cm^{-1} (CO). ^{1}H NMR(DMSO-d_6): $\delta = 2.4$, 2.6, 2.9 (3s, 9H, $3CH_3$), 3.8 (s, 2H, CH_2), 6.4 (s, 2H, NH_2), 6.9 (s, 1H, CH-pyridine).

Anal. calcd. for $C_{15}H_{14}N_4OS$(298.37): C, 60.38; H, 4.73; N, 18.78; S, 10.75%. Found: C, 60.53; H, 4.50; N, 18.61; S, 11.00%.

3-Aceylamino-2-bromomethyl-4,6-dimethylthieno [2,3-b]pyridine (18)

To a solution of compound **13b** (1.17 g, 0.005 mol) in acetic acid (30 mL), bromine (0.8 g, 5 mmol) in acetic acid (10 mL) was added dropwise during 10 min. The stirring was continued for 1 h. The solid product was collected, dissolved in water (100 mL), and neutralized with sodium carbonate solution (10%). The solid product was filtered off and recrystallized from pet. ether 60–80°C as white crystals 1.0 g (65%), m.p. 72°C.

IR: $\nu = 3260$ cm^{-1} (NH), 1670 cm^{-1} (CO). ^{1}H NMR ($CDCl_3$): $\delta = 2.3$, 2.6, 2.9 (2s, 6H, $2CH_3$), 4.3 (s, 2H, CH_2Br), 6.9 (s, 1H, CH-pyridine), 9.95 (s, 1H, NH).

Anal. calcd. for $C_{12}H_{13}BrN_2OS$ (313.21): C, 46.02; H, 4.18; Br, 25.51; N, 8.94; S, 10.24%. Found: C, 45.79; H, 4.33; Br, 25.28; N, 9.18; S, 10.00%.

3-Aryledineamino-2,4,6-trimethylthieno[2,3-b]pyridine (19)

A mixture of compound **11b** (0.96 g, 5 mmol) and aromatic aldehyde (0.005 mol) in ethanol (20 mL) was refluxed for 5 h and then allowed to cool. The solid product was collected and recrystallized from ethanol.

19a; produced 1.17 g (72%), m.p. 172–174°C.

IR: $\nu = 3050$ cm^{-1} (CH aromatic), 2950 cm^{-1} (CH aliphatic), 1630 cm^{-1} (C=N). ^{1}H NMR ($CDCl_3$): 2.4, 2.7, 3.0 (3s, 9H, $3CH_3$), 7.05 (s, 1H, CH-pyridine), 7.7, 7.9 (2d, 4H, CH-aromatic) and 8.6 (s, 1H, -CH=N).

Anal. calcd. for $C_{17}H_{15}N_3O_2S$(325.39): C, 62.75; H, 4.65; N, 12.91; S, 9.85%. Found: C, 62.58; H, 4.87; N, 13.14; S, 10.08%.

19b; produced 1.11 g (69%), 220°C.

IR: $\nu = 3050$ cm^{-1} (CH aromatic), 2950 cm^{-1} (CH aliphatic), 1630 cm^{-1} (C=N). ^{1}H NMR($CDCl_3$): 2.4, 2.6, 2.9 (3s, 9H, $3CH_3$), 3.0 (s, 6H, $2CH_3$), 6.95 (s, 1H, CH-pyridine), 7.3, 7.5 (2d, 4H, CH-aromatic) and 8.4 (s, 1H, -CH=N).

Anal. calcd. for $C_{19}H_{21}N_3S$(323.46): C, 70.55; H, 6.54; N, 12.99; S, 9.91%. Found: C, 70.33; H, 6.87; N, 13.20; S, 10.12%

19c; produced 1.16 g (74%), m.p.

IR: $\nu = 3050$ cm^{-1} (CH aromatic), 2950 cm^{-1} (CH aliphatic), 1630 cm^{-1} (C=N). ^{1}H NMR($CDCl_3$): 2.35, 2.6, 2.9 (3s, 9H, $3CH_3$), 6.95 (s, 1H, CH-pyridine), 7.3, 7.5 (2d, 4H, CH-aromatic) and 8.4 (s, 1H, -CH=N).

Anal. calcd. for $C_{17}H_{15}ClN_{2S}S$(314.84): C, 64.86; H, 4.80; Cl, 11.26; N, 8.90; S, 10.18%. Found: C, 65.08; H, 5.03; Cl, 11.03; N, 9.12; S, 10.00%.

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