New Fused Pyrazines. Synthesis of Pyrido[3',2':4,5]-thieno[2,3-*e*]pyrrolo[1,2-*a*]pyrazine Derivatives

H. S. El-Kashef, A. M. Kamal El-Dean and A. A. Geies

Chemistry Department, Faculty of Science, Assiut University, Assiut 71516, Egypt

J. C. Lancelot, P. Dallemagne* and S. Rault

Centre d'Etudes et de Recherche sur le Médicament de Normandie,
U.F.R. des Sciences Pharmaceutiques, 1- rue Vaubénard, 14032 Caen, France

Received January 1, 2000

The synthesis of the title compounds was achieved using the key intermediate ethyl 4,6-dimethyl-3-(pyrrol-1-yl)thieno[2,3-*b*]pyridine-2- carboxylate **2**. This latter compound was obtained *via* the interaction of the thienopyridine amino ester **1** with 2,5 dimethoxytetrahydrofuran in acidic medium.

J. Heterocyclic Chem., **37**, 1521 (2000).

The only report concerning the synthesis of benzothieno[2,3-*e*]pyrrolo[1,2-*a*]pyrazines was published by Robba and his group [1,2]. Now we are involved in a program dealing with the synthesis of the aza and diaza isosteres of these foregoing compounds [3-5]. As part of this program, we report herein the synthesis of the new tetracyclic heterocyclic system namely pyrido[3',2':4,5]-thieno[2,3-*e*]pyrrolo[1,2-*a*]pyrazine and other related derivatives.

Ethyl 3-amino-4,6-dimethylthieno[2,3-*b*]pyridine-3-carboxylate **1** [6] was allowed to react with 2,5-dimethoxytetrahydrofuran in boiling acetic acid to give the corresponding ethyl 4,6-dimethyl-3-(pyrrol-1-yl)thieno[2,3-*b*]pyridine-2-carboxylate **2**. The ester grouping of **2** was easily transformed into an acid hydrazide function, upon reaction with hydrazine hydrate in boiling ethanol, to give the acid hydrazide **3**. The latter compound gave the arylidene carboxyhydrazides **4a-d** by condensation with the corresponding aldehydes.

The acid hydrazide **3** proved to be a useful key intermediate in the synthesis of several heterocyclic nuclei. Thus, when **3** was reacted with carbon disulfide in refluxing pyridine, the product was the 4,6-dimethyl-2-(5-mercapto-oxadiazol-2-yl)-3-(pyrrol-1-yl)thieno-[2,3-*b*]pyridine **5**. This mercapto compound gave the corresponding *S*-alkyl derivatives **6a-d** when allowed to react with alkyl halides (Scheme 1).

On the other hand, the reaction of the carboxyhydrazide **3** with nitrous acid gave the acid azide **7**. When this acid azide was subjected to Curtius rearrangement in boiling alcohols (benzyl- or butyl alcohol) or in boiling xylene, in the presence of amines (butyl-, cyclohexyl-, benzyl-, or 2-hydroxyethylamine), the corresponding carbamates **8a,b** or the substituted ureas **9a-d** were obtained respectively. However, heating the acid azide **7** in refluxing inert solvent of high boiling point, such as xylene, in the absence of any reactive entity, the pyrazinone **10** was obtained. Thionation of the latter compound was undertaken using phosphorus pentasulfide in boiling pyridine to give the thione derivative **11** (Scheme 2).

The 4-hydrazino-8,10-dimethylpyrido[3',2':4,5]thieno-[2,3-*e*]pyrrolo[1,2-*a*]pyrazine **12** was obtained upon the treatment of compound **11** with hydrazine hydrate in refluxing pyridine. The hydrazino compound **12** was also found to be a versatile intermediate in the synthetic realizations of heterocyclic systems (Scheme 2). The reaction of **12** with benzaldehyde gave the corresponding hydrazone **13**. Its condensation with acetyl acetone gave the corresponding pyrazolyl derivative **14**. Upon heating in acetic anhydride the hydrazine **12** gave the triazolo compound **15**, and upon heating with triethylorthoformate in refluxing methanol and in presence of drops of acetic acid, the triazolo derivative **16** was obtained. On the other hand, when **12** was reacted with carbon disulfide in pyridine, the mercaptotriazolo derivative **17** was produced. The tetrazolo derivative **18** was obtained when **12** was treated with nitrous acid.

EXPERIMENTAL

All melting points were uncorrected and were determined on a Kofler melting point apparatus. The ir spectra were recorded on a Pye Unicam SP 300 spectrometer using KBr Wafer technique. ^{1}H nmr spectra were recorded on a 90 MHz Varian EM 390 nmr spectrometer using TMS as an internal standard. The chemical shifts were expressed as δ part per million. Elemental analyses were performed using a Perkin-Elmer 240 C Microanalyzer.

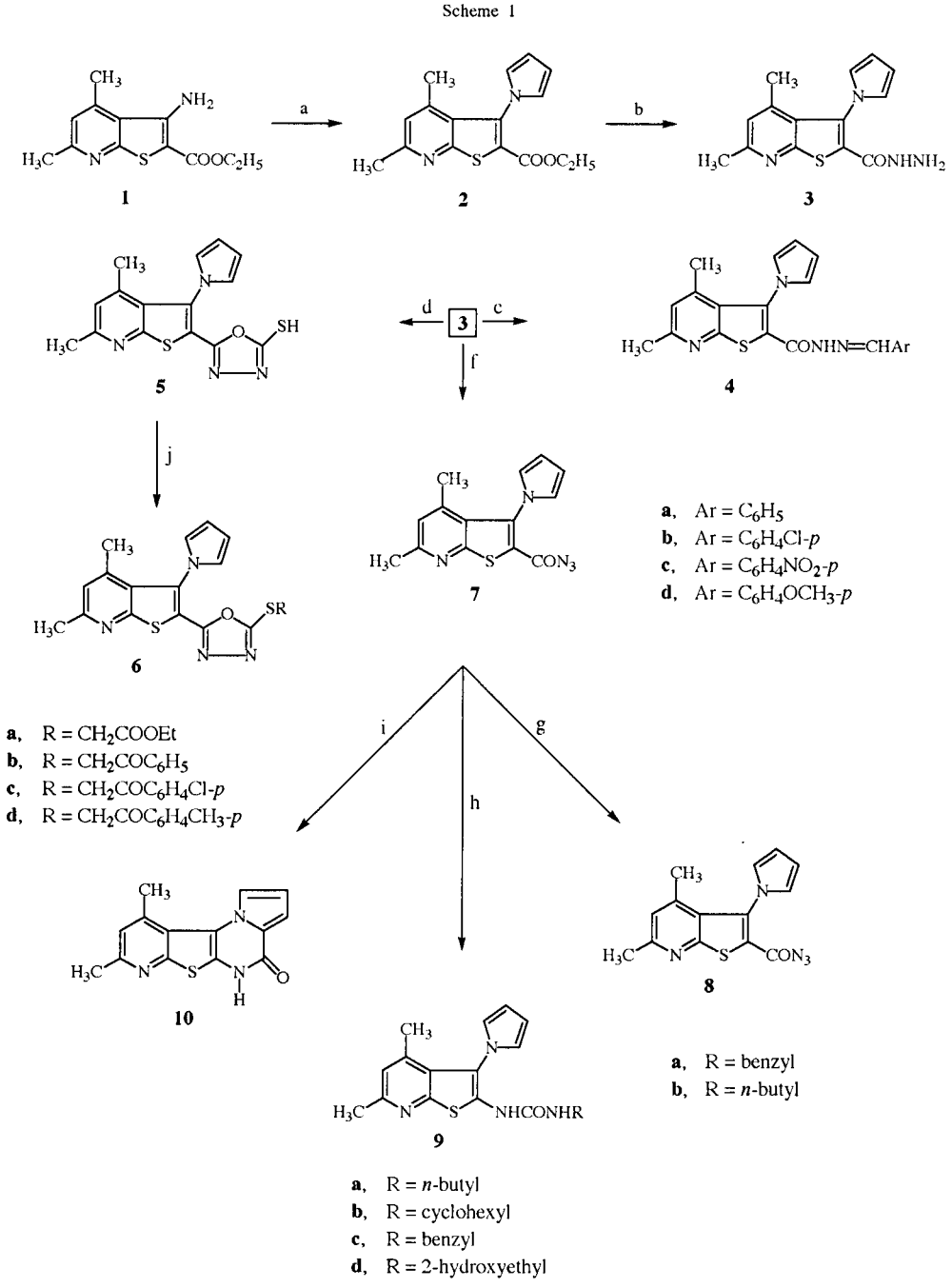
Ethyl 4,6-Dimethylthieno[2,3-*b*]pyridine-2-carboxylate (**1**).

This compound was synthesized according to a known procedure [6].

Ethyl 4,6-Dimethyl-3-(pyrrol-1-yl)thieno[2,3-*b*]pyridine-2-carboxylate (**2**).

A mixture of compound **1** (2.5 g, 0.01 mol) and dimethoxytetrahydrofuran (1.42 ml, 0.011 mol) in acetic acid (30 ml) was refluxed for 1 hour. After cooling, the solid precipitate was collected and recrystallized from ethanol as white crystals, 2.55 g

Scheme 1



a, DMTHF/AcOH; b, NH_2NH_2; c, ArCHO; d, CS_2/pyridine; e, RCl/NaOAc; f, $NaNO_2$/AcOH; g, ROH/heat; h, RNH_2/xylene/heat; i, xylene/heat; j, RX

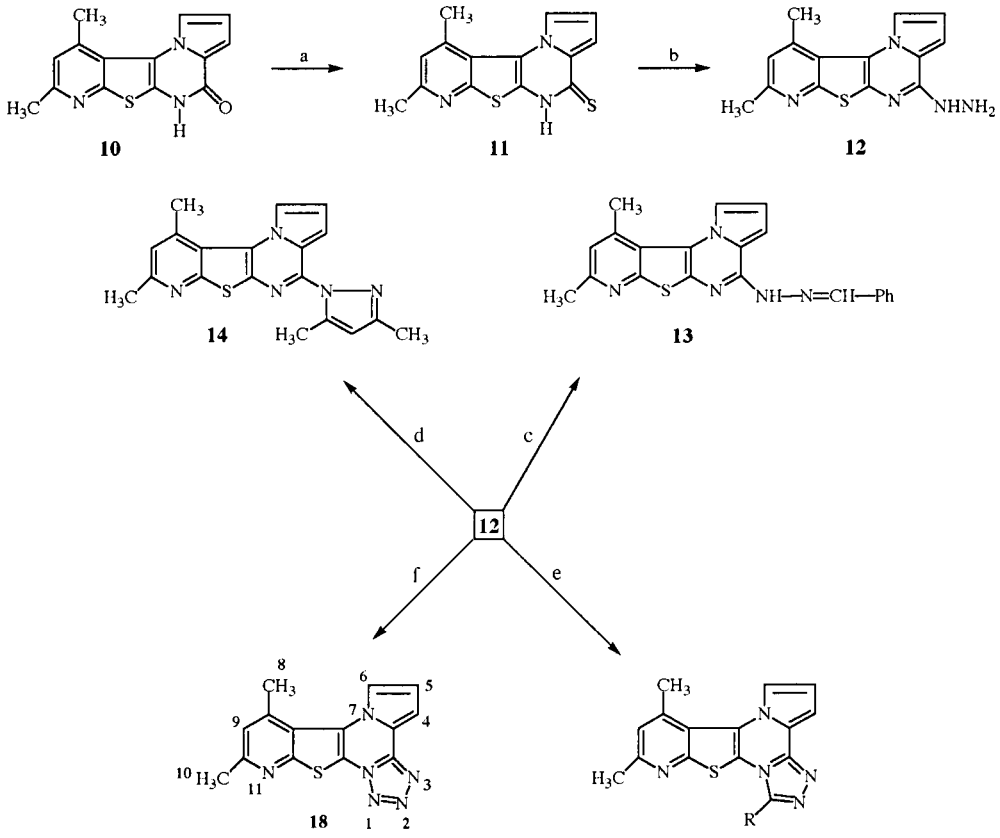
(85%), mp 147-149 °C; ir: ν 1730 (C=O) cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.10 (t, 3H, CH_3 ester), 2.50 (s, 3H, CH_3), 3.13 (s, 3H, CH_3), 3.93 (q, 2H, CH_2 ester), 6.30 (t, 2H, H3', H4' pyrrole), 6.90 (t, 2H, H2', H5' pyrrole) and 7.06 (s, 1H, CH pyridine).

Anal. Calcd. for $C_{16}H_{16}N_2O_2S$: C, 63.98; H, 5.37; N, 9.33; S, 10.67. Found: C, 64.21; H, 5.50; N, 9.09; S, 10.48.

4,6-Dimethyl-3-(pyrrol-1-yl)thieno[2,3-*b*]pyridine-2-carboxyhydrazide (**3**).

A mixture of compound **2** (3 g, 0.01 mol) and hydrazine hydrate (99%) (1 ml, 0.02 mol) in ethanol (40 ml) was heated under reflux for 4 hours. The reaction mixture was then allowed to cool, and the solid product was collected and recrystallized

Scheme 2



a, P_2S_5/pyridine; b, NH_2NH_2; c, PhCHO; d, Ac_2CH_2;
e, 15, Ac_2O, 16, $CH(OEt)_3$, 17, P_2S_5/pyridine; f, $NaNO_2$/AcOH

from ethanol as white crystals, 2.2 g (77.8%), mp 222 °C; ir: ν 3300, 3100 ($NHNH_2$), 1670 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.50 (s, 3H, CH_3), 3.10 (s, 3H, CH_3), 4.33 (s, 2H, NH_2), 6.11 (t, 2H, H3', H4' pyrrole), 6.80 (t, 2H, H2', H5' pyrrole), 6.90 (s, 1H, CH pyridine) and 7.66 (s, 1H, NH).

Anal. Calcd. for $C_{14}H_{14}N_4OS$: C, 58.72; H, 4.93; N, 19.57; S, 11.20. Found: C, 58.66; H, 5.10; N, 19.54; S, 11.04.

Arylidene 4,6-Dimethyl-3-(pyrrol-1-yl)thieno[2,3-*b*]pyridine-2-carboxyhydrazide (**4a-d**).

A mixture of equimolar amounts (0.005 mol) of compound **3** and the appropriate aromatic aldehyde in ethanol (25 ml) was refluxed for 3 hours. After cooling, the solid precipitate was collected and recrystallized from acetic acid.

Benzylidene 4,6-Dimethyl-3-(pyrrol-1-yl)thieno[2,3-*b*]pyridine-2-carboxyhydrazide (**4a**).

This compound was obtained as yellow crystals, 1.4 g (74.7%) mp 258-260 °C; ir: ν 3250 (NH), 1690 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.5 (s, 3H, CH_3), 3.21 (s, 3H, CH_3), 6.50 (t, 2H, H3', H4' pyrrole), 7.10 (t, 2H, H2', H5' pyrrole), 7.0-7.4 (m, 5H, phenyl), 7.13 (s, 1H, CH pyridine), 8.11 (s, 1H, CH=N), 11.20 (s, 1H, NH).

Anal. Calcd. for $C_{21}H_{18}N_4OS$: C, 67.36; H, 4.85; N, 14.96; S, 8.56. Found: C, 67.54; H, 5.08; N, 15.12; S, 8.32.

4-Chlorobenzylidene 4,6-Dimethyl-3-(pyrrol-1-yl)thieno-[2,3-*b*]pyridine-2- carboxyhydrazide (**4b**).

This compound was obtained as yellow crystals, 1.7 g (83.1%), mp >300 °C; ir: ν 3310 (NH), 1685 (C=O) cm^{-1}; ^1H nmr (CF_3COOD): δ 2.45 (s, 3H, CH_3), 3.03 (s, 3H, CH_3), 6.83 (t, 2H, H3', H4' pyrrole), 7.06 (t, 2H, H2', H5' pyrrole), 7.33 (s, 1H, CH pyridine), 7.40 (dd, 4H, ArH), 8.45 (s, 1H, CH=N).

Anal. Calcd. for $C_{21}H_{17}N_4OSCl$: C, 61.38; H, 4.19; N, 13.70; S, 7.84; Cl, 8.67. Found: C, 61.46; H, 3.98; N, 13.94; S, 8.06; Cl, 8.46.

4-Nitrobenzylidene 4,6-Dimethyl-3-(pyrrol-1-yl)thieno-[2,3-*b*]pyridine-2- carboxyhydrazide (**4c**).

This compound was obtained as yellow crystals, 1.8 g (85.8%), mp >300 °C; ir: ν 3250 (NH), 1690 (C=O), 1510 and 1330 (NO_2) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.53 (s, 3H, CH_3), 3.20 (s, 3H, CH_3), 6.50 (t, 2H, H3', H4' pyrrole), 6.93(t, 2H, H2', H5' pyrrole), 7.10 (s, 1H, CH pyridine), 7.15 (dd, 4H, ArH), 8.40 (s, 1H, CH=N), 12.20 (s, 1H, NH).

Anal. Calcd. for $C_{21}H_{17}N_5O_3S$: C, 60.13; H, 4.09; N, 16.70; S, 7.64. Found: C, 60.22; H, 3.88; N, 16.79; S, 7.86.

4-Methoxybenzylidene 4,6-Dimethyl-3-(pyrrol-1-yl)thieno-[2,3-*b*]pyridine-2-carboxyhydrazide (**4d**).

This compound was obtained as yellow crystals, 1.75 g (86.5%), mp 260-262 °C; ir: ν 3240 (NH), 1690 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.5 (s, 3H, CH_3), 2.9 (s, 3H, CH_3), 3.33 (s, 3H, CH_3O-), 6.50 (t, 2H, H3', H4' pyrrole), 7.00 (t, 2H, H2', H5' pyrrole), 7.10 (s, 1H, CH pyridine), 7.16 (dd, 4H, ArH), 8.35 (s, 1H, CH=N), 12.10 (s, 1H, NH).

Anal. Calcd. for $C_{22}H_{20}N_4O_2S$: C, 65.33; H, 4.99; N, 14.96; S, 8.56. Found: C, 67.54; H, 5.08; N, 15.12; S, 8.32.

4,6-Dimethyl-2-(5-mercapto-oxadiazol-2-yl)-3-(pyrrol-1-y1)-thieno[2,3-*b*]pyridine (**5**).

A mixture of the carboxyhydrazide **3** (2.86 g, 0.01 mol) and carbon disulfide (3 ml) in pyridine (15 ml) was heated on a water bath under reflux for 6 hours. The excess of carbon disulfide was then eliminated under reduced pressure and the residue was poured into cold water (100 ml). The resulting mixture was acidified with diluted hydrochloric acid andt he solid precipitate was collected and recrystallized from ethanol as white crystals, 2.3 g (70%), mp 255-257 °C; ir: ν 2690 (SH) cm^{-1}; ^1H nmr (DMSO d_6): δ 2.3 (s, 3H, CH_3) 3.1 (s, 3H, CH_3), 4.0 (s, 1H, SH), 6.2 (t, 2H, H3', H4' pyrrole),6.83 (t, 2H, H2', H5' pyrrole) and 7.0 (s, 1H, CH pyridine).

Anal. Calcd. for $C_{15}H_{12}N_4OS_2$: C, 54.86; H, 3.68; N, 17.06; S, 19.53. Found: C, 55.04; H, 3.72; N, 16.90; S, 19.34.

General Procedure for the Preparation of 4,6-Dimethyl-2-(5-substitutedmercapto-oxadiazol-2-yl)-3-(pyrrol-1-yl)thieno-[2,3-*b*]pyridine (**6a-e**).

A mixture of **5** (3.28 g, 0.01 mol), the appropriate halide (0.01 mol) and sodium acetate (0.012 mol) in ethanol (30 ml) was heated under reflux for 1 hour. After cooling, the solid product was collected by filtration, washed with water and recrystallized from ethanol.

4,6-Dimethyl-2-(5-ethoxycarbonylmethylthioxadiazol-2-yl)-3-(pyrrol-1-yl)thieno[2,3-*b*]pyridine (**6a**).

This compound was obtained as fluffy white needles, 3.75 g (86.1%), mp 110-112 °C; ir: ν 1740 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.53 (t, 3H, CH_3 ester) 2.50 (s, 3H, CH_3), 3.16 (s, 3H, CH_3), 3.53 (q, 2H, CH_2 ester), 4.21 (s, 2H, SCH_2), 6.50 (t, 2H, H3', H4' pyrrole), 6.90 (t, 2H, H2', H5' pyrrole), 7.06 (s, 1H, CH pyridine).

Anal. Calcd. for $C_{19}H_{18}N_4O_3S_2$: C, 55.06; H, 4.38; N, 13.52; S, 15.47. Found: C, 55.18; H, 4.52; N, 13.68; S, 15.60.

4,6-Dimethyl-2-(5-benzoylmethylthioxadiazol-2-yl)-3-(pyrrol-1-yl)thieno[2,3-*b*]pyridine (**6b**).

This compound was obtained as fluffy yellow needles, 3.7 g (82.8%), mp 220-222 °C; ir: ν 1680 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.87 (s, 3H, CH_3) 2.57 (s, 3H, CH_3), 4.83 (s, 2H, SCH_2), 6.06 (t, 2H, H3', H4' pyrrole), 6.86 (t, 2H, H2', H5' pyrrole), 7.13 (s, 1H, CH pyridine), 7.57 (m, 3H, ArH), 8.17 (m, 2H, ArH).

Anal. Calcd. for $C_{23}H_{18}N_4O_2S_2$: C, 61.87; H, 4.06; N, 12.55; S, 14.36. Found: C, 62.01; H, 3.85; N, 12.69; S, 14.60.

4,6-Dimethyl-2-[5-(4-chlorobenzoylmethylthioxadiazol-2-yl)]-3-(pyrrol-1-yl)thieno[2,3-*b*]pyridine (**6c**).

This compound was obtained as fluffy buff needles, 4.1 g (83.2%), mp 210-212 °C; ir: ν 1680 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.83 (s, 3H, CH_3) 2.43 (s, 3H, CH_3), 4.76 (s, 2H, SCH_2), 6.06 (t, 2H, H3', H4' pyrrole), 6.86 (t, 2H, H2', H5' pyrrole), 7.16 (s, 1H, CH pyridine), 7.76 (dd, 4H, ArH).

Anal. Calcd. for $C_{23}H_{17}N_4O_2S_2Cl$: C, 57.43; H, 3.56; N, 11.65; S, 13.33; Cl, 7.37. Found: C, 57.53; H, 3.42; N, 11.69; S, 13.20; Cl, 7.30.

4,6-Dimethyl-2-[5-(4-methylbenzoylmethylthioxadiazol-2-yl)]-3-(pyrrol-1-yl)thieno[2,3-*b*]pyridine (**6d**).

This compound was obtained as fluffy cream needles, 3.8 g (82.5%), mp 200-202 °C; ir: ν 1690 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.76 (s, 3H, CH_3) 2.33 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 4.70 (s, 2H, SCH_2), 5.96 (t, 2H, H3', H4' pyrrole), 6.76 (t, 2H, H2', H5' pyrrole), 7.03 (s, 1H, CH pyridine), 7.49 (dd, 4H, ArH).

Anal. Calcd. for $C_{24}H_{20}N_4O_2S_2$: C, 62.59; H, 4.38; N, 12.16; S, 13.93. Found: C, 62.63; H, 4.52; N, 12.25; S, 14.06.

4,6-Dimethyl-3-(pyrrol-1-yl)thieno[2,3-*b*]pyridine-2-carboxyazide (**7**).

To a solution of compound **3** (2.86 g, 0.01 mol) in acetic acid (30 ml), cooled to 5 °C, a cold solution of sodium nitrite (0.69 g, 0.01 mol in 2 ml H_2O) was added dropwise with stirring. After the completion of the addition, the reaction mixture was stirred at room temperature for 1 hour. The solid product was filtered, washed abundantly with cold water and air dried. It was used without any further purification, mp 110 °C dec, 2.4 g (80.7%); ir: ν 2120 (N3), 1720 (C=O) cm^{-1}; ^1H nmr ($CDCl_3$): δ 2.53 (s, 3H, CH_3), 3.20 (s, 3H, CH_3), 6.20 (t, 2H, H3', H4' pyrrole), 6.90 (t, 2H, H2', H5' pyrrole), 7.13 (s, 1H, CH pyridine).

General Procedure for the Preparation of the Carbamates (**8a,b**).

A sample of the azide **7** (1.49 g, 0.005 mol) in alcohol (benzyl or isopropyl alcohol, 6 ml) was heated under reflux for 2 hours then allowed to cool. The solid precipitate was filtered, dried and recrystallized from the same alcohol.

Benzyl *N*-[4,6-Dimethyl-3-(pyrrol-1-yl)thieno[2,3-*b*]pyridine-2-yl]carbamate (**8a**).

This compound was obtained as pale yellow crystals, 1.64 g (86.8%), mp 190-192 °C; ir: ν 3370 (NH), 1700 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.30 (s, 3H, CH_3), 3.0 (s, 3H, CH_3), 4.81 (s, 2H, CH_2), 6.08 (t, 2H, H3', H4' pyrrole), 6.61 (t, 2H, H2', H5' pyrrole), 6.93 (s, 1H, CH pyridine), 7.20 (m, 5H, phenyl), 9.73 (s, 1H, NH).

Anal. Calcd. for $C_{21}H_{19}N_3O_2S$: C, 66.82; H, 5.42; N, 11.50; S, 8.77. Found: C, 66.91; H, 5.51; N, 11.68; S, 8.92.

Butyl *N*-[4,6-Dimethyl-3-(pyrrol-1-yl)thieno[2,3-*b*]pyridin-2-yl]carbamate (**8b**).

This compound was obtained as pale yellow crystals, 1.5 g (87.4%), mp 210-212 °C; ir: ν 3400 (NH), 1710 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.63 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 2.51 (m, 4H, $2CH_2$), 2.93 (s, 3H, CH_3), 4.10 (m, 2H, OCH_2-), 6.43 (t, 2H, H3', H4' pyrrole), 6.91 (t, 2H, H2', H5' pyrrole), 7.10 (s, 1H, CH pyridine), 7.20 (m, 5H, phenyl), 9.06 (s, 1H, NH).

Anal. Calcd. for $C_{18}H_{21}N_3O_2S$: C, 62.95; H, 6.16; N, 12.23; S, 9.33. Found: C, 62.86; H, 6.22; N, 12.08; S, 9.28.

General Procedure for the Preparation of the Urea Derivatives (**9a-d**).

A mixture of equimolar amounts (0.005 mol) of the azide **7** and appropriate amine in xylene (10 ml) was heated under reflux for 1 hour. After cooling, the solid product was collected and recrystallized from ethanol.

N-Butyl-*N'*-[3-(pyrrol-1-yl)-4,6-dimethylthieno[2,3-*b*]pyridin-2-yl]urea (**9a**).

This compound was obtained as fluffy white needles, 1.33 g (77.7%), mp 168-170 °C; ir: ν 3400 (NH), 1640 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 0.83 (s, 3H, CH_3), 1.22 (m, 4H, $2CH_2$), 1.76 (s, 3H, CH_3), 2.53 (s, 3H, CH_3), 3.12 (q, 2H, NCH_2), 6.20 (b, 2H, 2NH), 6.46 (t, 2H, H3', H4' pyrrole), 7.06 (t, 2H, H2', H5' pyrrole), 7.23 (s, 1H, CH pyridine).

Anal. Calcd. for $C_{18}H_{22}N_4OS$: C, 63.13; H, 6.48; N, 16.36; S, 9.36. Found: C, 62.94; H, 6.58; N, 16.50; S, 9.14.

N-Cyclohexyl-*N'*-[3-(pyrrol-1-yl)-4,6-dimethylthieno-[2,3-*b*]pyridin-2-yl]urea (**9b**).

This compound was obtained as fluffy cream needles, 1.4 g (76%), mp 184-186 °C; ir: ν 3380 (NH), 1650 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 0.83-1.70 (m, 10H, $5CH_2$), 1.83 (s, 3H, CH_3), 2.57 (s, 3H, CH_3), 3.80 (m, 1H, CH), 5.93 (b, 1H, NH), 6.40 (t, 2H, H3', H4' pyrrole), 7.10 (t, 2H, H2', H5' pyrrole), 7.13 (s, 1H, CH pyridine), 9.12 (b, 1H, NH).

Anal. Calcd. for $C_{20}H_{24}N_4OS$: C, 65.19; H, 6.56; N, 15.20; S, 8.70. Found: C, 65.10; H, 6.65; N, 15.09; S, 8.94.

N-Benzyl-*N'*-[3-(pyrrol-1-yl)-4,6-dimethylthieno[2,3-*b*]pyridin-2-yl]urea (**9c**).

This compound was obtained as fluffy cream needles in 78%, mp 177-179 °C; ir: ν 3280 (NH), 1670 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.80 (s, 3H, CH_3), 2.50 (d, 2H, CH_2), 3.20 (s, 3H, CH_3), 6.33 (t, 2H, H3', H4' pyrrole), 6.92 (t, 2H, H2', H5' pyrrole), 7.03 (s, 1H, CH pyridine), 10.43 (s, 1H, NH), 11.50 (s, 1H, NH).

Anal. Calcd. for $C_{21}H_{20}N_4OS$: C, 76.00; H, 5.35; N, 14.88; S, 8.52. Found: C, 76.11; H, 5.39; N, 14.85; S, 8.60.

N-(2-Hydroxyethyl)-*N'*-[3-(pyrrol-1-yl)-4,6-dimethylthieno-[2,3-*b*]pyridin-2-yl]urea (**9d**).

This compound was obtained as yellow needles (80%), mp 156-158 °C; ir: ν 3390 (NH), 1640 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.87 (s, 2H, CH_2), 2.53 (s, 3H, CH_3), 3.23 (s, 2H, CH_2), 3.33 (s, 3H, CH_3), 4.56 (s, 1H, OH), 6.26 (t, 2H, H3', H4' pyrrole), 7.07 (t, 2H, H2', H5' pyrrole), 7.17 (s, 1H, CH pyridine), 10.13 (s, 1H, NH), 10.80 (s, 1H, NH).

Anal. Calcd. for $C_{16}H_{18}N_4OS$: C, 58.16; H, 5.49; N, 16.96; S, 9.70. Found: C, 58.25; H, 5.50; N, 16.80; S, 9.81.

8,10-Dimethylpyrido[3',2':4,5]thieno[2,3-*e*]pyrrolo-[1,2-*a*]pyrazine-4-(5*H*)one (**10**).

A sample of compound **7** (2.97 g, 0.01 mol) in xylene (50 ml) was heated under reflux for 1 hour. After cooling the solid product was collected and recrystallized from DMF as buff crystals, 2.4 g (89%), mp >300 °C; ir: ν 3150 (NH) and 1670 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.53 (s, 3H, CH_3), 2.93 (s, 3H, CH_3), 6.60 (dd, 1H, H1), 6.9 (s, 1H, CH pyridine), 7.10 (dd, 1H, H3), 7.90 (dd, 1H, H2), 10.5 (s, 1H, NH).

Anal. Calcd. for $C_{14}H_{11}N_3OS$: C, 62.43; H, 4.12; N, 15.60; S, 11.90. Found: C, 62.51; H, 3.02; N, 15.42; S, 12.10.

8,10-Dimethylpyrido[3',2':4,5]thieno[2,3-*e*]pyrrolo-[1,2-*a*]pyrazin-4-(5*H*)thione (**11**).

A mixture of compound **10** (2.69 g, 0.01 mol) and phosphorus pentasulfide (4.44 g, 0.01 mol) in pyridine (40 ml) was heated under reflux for 6 hours. After cooling the reaction mixture was poured into cold water and acidified with acetic acid. The solid product thus obtained was filtered, washed with water, dried and recrystallized from DMF as yellow crystals, 2.2 g (77%), mp >300 °C; ir: ν 3150 (NH), 1270 (C=S) cm^{-1}; ^1H nmr (DMSO d_6): δ 2.50 (s, 3H, CH_3), 2.90 (s, 3H, CH_3), 6.53, (dd, 1H, H2), 7.13 (dd, 1H, H3), 7.13 (dd, 1H, H3), 6.9 (s, 1H, CH pyridine), 13.5 (s, 1H, NH).

Anal. Calcd. for $C_{14}H_{11}N_3S_2$: C, 58.92; H, 3.88; N, 14.72; S, 22.48. Found: C, 58.83; H, 4.00; N, 14.79; S, 22.57.

4-Hydrazino-8,10-dimethylpyrido[2',3':4,5]thieno-[2,3-*b*]pyrrolo[1,2-*d*]pyrazine (**12**).

A mixture of **11** (2.85 g, 0.01 mol) and hydrazine hydrate (99%), (0.56 ml, 0.015 mol) in pyridine (30 ml) was refluxed for 6 hours till the evolution of H_2S gas ceased. After cooling, the solid precipitate was filtered and recrystallized from pyridine as yellow needles, mp 260-262 °C; yield 70%; ir: ν 3320, 3200 ($NHNH_2$) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.40 (s, 3H, CH_3), 3.20 (s, 3H, CH_3), 4.40 (s, 2H, NH_2), 6.45 (dd, 1H, H2), 6.60 (dd, 1H, H3), 7.15 (dd, 1H, H1), 7.45 (s, 1H, CH pyridine), and 8.81 (s, 1H, NH).

Anal. Calcd. for $C_{14}H_{13}N_5S$: C, 59.34; H, 4.62; N, 24.72; S, 11.31. Found: C, 59.39; H, 4.57; N, 24.88; S, 11.22.

Benzyliden 8,10-Dimethylpyrido[2',3':4,5]thieno[2,3-*b*]pyrrolo-[1,2-*d*]pyrazin-4-ylhydrazine (**13**).

A mixture of **12** (1.41 g, 0.005 mol) and benzaldehyde (0.51 ml, 0.005 mol) in ethanol (20 ml) was heated under reflux for 1 hour. After cooling, the solid product was collected and recrystallized from ethanol as yellow crystals, mp 250-252 °C (74%); ir: ν 3250 (NH), 1630 (C=N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.50 (s, 3H, CH_3), 3.23 (s, 3H, CH_3), 6.50 (dd, 1H, H2), 6.73 (dd, 1H, H3), 7.30 (dd, 1H, H1), 7.45 (s, 1H, CH pyridine), 7.45 (m, 5H, phenyl), 8.40 (s, 1H, CH=N) and 12.43 (s, 1H, NH).

Anal. Calcd. for $C_{21}H_{17}N_5S$: C, 67.90; H, 4.61; N, 18.85; S, 8.63. Found: C, 68.07; H, 4.45; N, 19.03; S, 8.50.

4-(3,5-Dimethylpyrazol-1-yl)-8,10-dimethylpyrido[2',3':4,5]-thieno[2,3-*b*] pyrrolo[1,2-*d*]pyrazine (**14**).

A mixture of compound **12** (1.41 g, 0.005 mol) and excess acetylacetone (2 ml) was heated at boiling for 1/2 hour, then ethanol (20 ml) was added and the reaction mixture was refluxed for an additional three hours. After cooling, the solid product was filtered and recrystallized from acetic acid as white crystals, 1.1 g (63.3%), mp 217-219 °C; ir: ν 1630 (C=N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.60 (s, H, CH_3), 2.91 (s, H, CH_3), 3.0 (s, H, CH_3), 3.30 (s, H, CH_3), 6.63 (dd, 1H, H2), 6.91 (s, 1H, CH pyridine), 7.43 (dd, 1H, H3) and 7.80 (dd, 1H, H1).

Anal. Calcd. for $C_{19}H_{17}N_5S$: C, 65.68; H, 4.93; N, 20.16; S, 9.23. Found: C, 65.63; H, 5.01; N, 20.15; S, 9.20.

6,10,12-Trimethylpyrido[3',2':4,5]thieno[2,3-*e*]pyrrolo[1,2-*a*]-1,2,4-triazolo[3,4-*c*]pyrazine (**15**).

A sample of compound **12** (1.41 g, 0.005 mol) was heated under reflux with acetic anhydride (5 ml) for 2 hours, then allowed to cool. The solid product was collected and recrystal-

lized from acetic acid as green crystals, 1.3 g (84.6%), mp 217-219 °C; ir: ν 1630 (C=N) cm^{-1}; ^1H nmr (CF_3COOD): δ 3.03 (s, 3H, CH_3), 3.16 (s, 3H, CH_3), 3.30 (s, 3H, CH_3), 7.16 (dd, 1H, H2), 7.86 (m, 2H, H3+CH pyridine), 8.46 (dd, 1H, H1).

Anal. Calcd. for $C_{16}H_{13}N_5S$: C, 62.52; H, 4.26; N, 22.78; S, 10.43. Found: C, 62.42; H, 4.08; N, 23.00; S, 10.64.

10,12-Dimethylpyrido[3',2':4,5]thieno[2,3-*e*]pyrrolo[1,2-*a*]-1,2,4-triazolo[3,4-*c*]pyrazine (**16**).

A mixture of compound **12** (1.41 g, 0.005 mol) and triethyl orthoformate (1.2 ml; 0.007 mol) in methanol (20 ml) containing a few drops of acetic acid was heated under refluxed for 4 hours. After cooling, the solid product was filtered and recrystallized from DMF as yellowish-white crystals, 1 g (68%), mp >300 °C; ir: ν 11620 (C=N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.51 (s, 3H, CH_3), 3.33 (s, 3H, CH_3), 7.16 (dd, 1H, H2), 7.86 (rn, 2H, H3+CH pyridine), 8.40 (dd, 1H, H1), 9.0 (s, 1H, CH triazole).

Anal. Calcd. for $C_{15}H_{11}N_5S$: C, 61.42; H, 3.78; N, 23.87; S, 10.93. Found: C, 61.49; H, 3.90; N, 23.90; S, 11.10.

10,12-Dimethylpyrido[3',2':4,5]thieno[2,3-*e*]pyrrolo[1,2-*a*]-1,2,4- triazolo[5,1-*c*]pyrazine (**17**).

A mixture of compound **12** (5.66 g, 0.02 mol) and CS_2 (2.5 ml) in pyridine (25 ml) was heated under reflux on a water bath for 8 hours. The excess carbon disulfide was eliminated under reduced pressure and the solid product was filtered and recrystallized from DMF as orange crystals, 4.9 g (75.3%), mp >300 °C ; ir: ν 3310 (NH), 1270 (C=S) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.30 (s, 3H, CH_3), 3.30 (s, 3H, CH_3), 6.73 (s, 1H, CH pyridine), 7.13 (dd, 1H, H2), 7.85 (dd, 1H, H3), 8.53 (dd, 1H, H1), 9.60 (s, 1H, NH).

Anal. Calcd. for $C_{15}H_{11}N_5S_2$: C, 55.37; H, 3.41; N, 21.52; S, 19.70. Found: C, 55.45; H, 3.51; N, 21.59; S, 19.62.

8,10-Dimethylpyrido[3',2':4,5]thieno[2,3-*e*]pyrrolo[1,2-*a*]-tetrazolo[5,1-*c*]pyrazine (**18**).

To a solution of **12** (0.005 mol) in acetic acid (30 ml), cooled to 5 °C, was added a solution of sodium nitrite (0.05 mol/5 ml H_2O) dropwise with stirring. After the completion of the addition, the reaction mixture was allowed to stand at room temperature for one hour and then diluted with cold water (50 ml). The solid precpitate was collected and recrystallized from ethanol as brown crystals (68%), mp 240-242 °C dec; ir: ν 1640 (C=N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.53 (s, 3H, CH_3), 3.23 (s, 3H, CH_3), 6.50 (dd, 1H, H4), 6.91 (s, 1H, CH pyridine), 7.33 (dd, 1H, H5), 7.80 (dd, 1H, H6).

Anal. Calcd. for $C_{14}H_{10}N_6S$: C, 57.13; H, 3.42; N, 28.55; S, 10.89. Found: C, 56.99; H, 3.46; N, 28.48; S, 11.00.

REFERENCES AND NOTES

[1] M. Cugnon de Sévricourt, H. El-Kashef, S. Rault and M. Robba, *Synthesis*, **9**, 710 (1981).

[2] H. S. El-Kashef, S. Rault, J. C. Lancelot and M. Robba, *J. Heterocydic Chem.*, **23**, 61, (1986).

[3] Sh. M. Radwan, M. S. Abbady and H. S. El-Kashef, *Phosphorus, Sulfur and Silicon*, **89**, 193 (1994).

[4] E. A. Bakhite, A. A. Geies, A. M. Kamal El-Dean and H. S. El-Kashef, *Phosphorus, Sulfur and Silicon*, **104**, 134 (1994).

[5] A. A. Geies, E. A. Bakhite and H. S. El-Kashef, *Pharmazie*, **53**, 686 (1998).

[6] V. I. Shvedov, T. P. Sycheva and T. V. Sakovich, *Khim. Geterotsikl. Soedin*, **10**, 1331 (1978); *Chem. Abstr.*, **92**, 76361 (1980).