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SYNTHESIS OF PYRIDO[3',2':4,5]THIENO[3,2-*d*]-[1,3,2]DIAZAPHOSPHORINE DERIVATIVES

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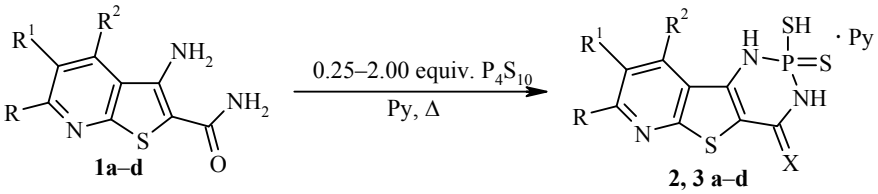
Refluxing 3-aminothieno[2,3-b]pyridine-2-carboxamides with P_4S_{10} in dry pyridine gave the substituted 2-mercapto-2,3-dihydropyrido[3',2':4,5]thieno[3,2-d][1,3,2]diazaphosphorin-4(1H)-one-2-thiones and/or -2,4(1H)-dithiones as 1:1 complexes with pyridine.

Keywords: 1,3,2λ^5-diazaphosphorines, tetraphosphorus decasulfide, thieno[2,3-*b*]pyridines, thiophosphorylation.

Thieno[2,3-*b*]pyridines form a very numerous and accessible group of compounds with a broad spectrum of useful properties [1-4], which includes anti-inflammatory, antibacterial, anticancer and other types of activity. In recent times, thieno[2,3-*b*]pyridines have been actively used in the preparation of condensed analogs and of different functionalized derivatives [1-4]. 1,3,2λ^5-Diazaphosphorines are a relatively little studied class of compounds [5, 6]. They principally attract interest as aza analogs of known 1,3,2-oxazaphosphorine series anticancer drugs (cyclophosphamide, trofosfamide and its derivatives [7-9]). The data concerning the antitumor activity of 1,3,2-diazaphosphorines [9, 10] points to the possibility of promising developments in this area. In addition, condensed 1,3,2-diazaphosphorines have been seldom reported in the literature. Accessible 3-aminothieno[2,3-*b*]pyridine-2-carboxamides are convenient substrates for phosphorylation reactions, but similar reactions of thienopyridines have not been described, and phosphorus containing thieno[2,3-*b*]pyridine derivatives have not been reported to the current time.



1–3 a R+R^1 = (CH$_2$)$_3$, R^2 = 2-furyl; **b** R+R^1 = (CH$_2$)$_4$, R^2 = 4-BnOC$_6$H$_4$; **c** R+R^1 = (CH$_2$)$_4$, R^2 = H; **d** R = R^2 = Me, R^1 = H; **2a–d** X = O, **3a–d** X = S

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We have found that the 3-aminothienopyridine-2-carboxamides **1a**,**b**,**d** are readily thiophosphorylated using 0.25 equivalents of P_4S_{10} in refluxing absolute pyridine, to form the tetrahydropyrido[3',2':4,5]thieno-[3,2-*d*][1,3,2]diazaphosphorines **2a**,**b**,**d**, representing a novel heterocyclic system. The reaction was not conducted with compound **1c** under these conditions.

Using an excess of P_4S_{10} led to a mixture of compounds **2a-d** and the thionation products **3a-d** in variable proportions. It should be noted that the thiophosphorylation of *ortho*-aminocarboxamides with excess P_4S_{10} was almost always accompanied by full thionation, and products with a carbonyl function were very rarely found [11]. Full thionation in this case clearly required the use of at least equimolar amount of P_4S_{10}. Compounds **2**, **3a-d** form stable 1:1 solvates with pyridine, which agrees well with known data for benzo[1,3,2]diazaphosphorine derivatives [12]. Compounds **2**, **3a-d** are insoluble in ether and acetone, poorly soluble in pyridine, cold water, and ethanol, but soluble in DMSO and in hot water.

Hence treatment of 3-aminothieno[2,3-*b*]pyridine-2-carboxamides with P_4S_{10} in pyridine opens up possibilities for preparing pyrido[3',2':4,5]thieno[3,2-*d*][1,3,2]diazaphosphorine derivatives. The use of an excess of P_4S_{10} also provides an option for thionation of the substrate carbonyl group.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on Bruker DPX-400 (400 MHz) and DRX-500 (500 MHz) instruments using DMSO-d_6 with TMS as internal standard. The ^{13}C NMR spectra were recorded in heteronuclear decoupling mode on a Bruker DRX-500 (125 MHz) instrument using DMSO-d_6 with TMS as internal standard. The ^{31}P NMR spectra were recorded on a Varian VXR-300 (121 MHz) using 85% H_3PO_4 as external standard. HPLC-MS analysis was performed for compounds **2a** and **3c** using an Agilent 1100 chromato-mass spectrometer with diode array (UV, 215, 254, and 265 nm) and Agilent LC/MSD SL mass selective detectors with a Zorbax SB-C18 analytical column and with electrospray ionization at atmospheric pressure. HPLC-MS analysis of compounds **2b**,**d** and the mixtures of compounds **2b**+**3b** and **2d**+**3d** was performed on a Shimadzu LC-10AD liquid chromatograph with Shimadzu SP D-10A UV-Vis (254 nm) and Sedex 75 ELSD detectors combined with a PE SCIEX API 150EX mass spectrometer. Elemental analysis was carried out using a Carlo-Erba 1106 Elemental Analyzer. Melting points were determined on a Kofler hot stage apparatus, and were not corrected. The purity of the obtained compounds was monitored on Silufol UV-254 plates with acetone–hexane (1:1) as eluent and visualized using UV light and iodine vapor. Compounds **1c**,**d** have been reported in the literature [13, 14] and were prepared by alkylation of the corresponding 3-cyano-pyridine-2(1*H*)-thiones with 2-chloroacetamide with subsequent Thorpe–Ziegler cyclization of the *S*-alkyl derivatives using KOH in DMF.

3-Amino-4-(2-furyl)-6,7-dihydro-5*H*-cyclopenta[*b*]thieno[3,2-*e*]pyridine-2-carboxamide (1a). A 10% aqueous KOH solution (2.3 ml, 4.40 mmol) was added to a suspension of the 4-(2-furyl)-2-thioxo-2,5,6,7-tetra-hydro-1*H*-cyclopenta[*b*]pyridine-3-carbonitrile [15] (1.0 g, 4.13 mmol) in DMF (5 ml) and stirred at 70-80°C to full dissolution. 2-Chloroacetamide (0.4 g, 4.28 mmol) was added as a single aliquot to this solution, stirred for 30 min at 25°C, and heated to reflux. A further amount of the 10% aqueous KOH (2.3 ml, 4.40 mmol) was added, and the obtained mixture was refluxed with stirring for 2-3 min, cooled, diluted with EtOH (10 ml), and left overnight. The precipitate that formed was filtered off and washed with EtOH and water. Yield 0.8 g (65%). Fine, yellow-brown crystals. Mp >260ºC (decomp.). ^{1}H NMR spectrum (400 MHz), δ, ppm (*J*, Hz): 2.07-2.12 (2H, m, CH_2); 2.90-2.94 (2H, m, CH_2); 3.04-3.08 (2H, m, CH_2); 6.34 (2H, br. s, NH_2); 6.77-6.80 (1H, m, H-4 Fur); 6.91 (1H, br. d, *J* = 2.5, H-3 Fur); 7.20 (2H, br. s, $CONH_2$); 7.98 (1H, m, H-5 Fur). Found, %: C 60.34; H 4.30; N 14.19. $C_{15}H_{13}N_3O_2S$. Calculated, %: C 60.19; H 4.38; N 14.04.

3-Amino-4-[4-(benzyloxy)phenyl]-5,6,7,8-tetrahydrothieno[2,3-*b*]quinoline-2-carboxamide (1b) was prepared by modification of method [16]. A suspension of the 4-[4-(benzyloxy)phenyl]-2-thioxo-1,2,5,6,7,8-tetrahydroquinoline-3-carbonitrile (1.00 g, 2.69 mmol) in DMF (6 ml) was treated with 10%

aqueous KOH (1.5 ml, 2.89 mmol), and 2-chloroacetamide (0.26 g, 2.78 mmol) was added to the solution obtained. The suspension of the *S*-alkylated derivative was stirred for 1 h at 40°C, a further 10% aqueous KOH (1.5 ml) was added, and the mixture was refluxed with stirring for 3 min. The reaction mixture was maintained for 24 h at 20°C, the precipitate formed was filtered off and washed successively with EtOH, water, EtOH, and Et_2O. Yield 1.06 g (93%). Light-yellow powder. Mp 248-250°C. ^{1}H NMR spectrum (400 MHz), δ, ppm (*J*, Hz): 1.65-1.69 (2H, m, CH_2); 1.77-1.84 (2H, m, CH_2); 2.34-2.37 (2H, m, CH_2); 2.95-2.99 (2H, m, CH_2); 5.18 (2H, br. s, OCH_2); 5.62 (2H, br. s, NH_2); 7.07 (2H, br. s, $CONH_2$); 7.20 (2H, d, *J* = 8.7, H Ar); 7.26 (2H, d, *J* = 8.7, H Ar); 7.34-7.38 (1H, m, H-4 Ph); 7.42 (2H, dd, *J* = 7.3, *J* = 7.3, H-3,5 Ph); 7.50 (2H, d, *J* = 7.3, H-2,6 Ph). Found, %: C 70.04; H 5.47; N 9.89. $C_{25}H_{23}N_3O_2S$. Calculated, %: C 69.91; H 5.40; N 9.78.

Synthesis of Tetrahydropyrido[3',2':4,5]thieno[3,2-*d*][1,3,2]diazaphosphorines 2, 3 (General Method). Finely powdered thienopyridine **1a-d** (1-3 mmol) was dissolved with heating in absolute pyridine (4-5 ml). The indicated amount of P_4S_{10} was added in one aliquot to the solution obtained. The reaction mixture was refluxed for 1 h. Generally, even after 5-7 min a yellow, crystalline product began to precipitate. The suspension was cooled, poured into EtOH (15-20 ml), stirred for 3 h, filtered, and repeatedly washed with EtOH and acetone.

10-(2-Furyl)-2-mercapto-2-thioxo-2,3,8,9-tetrahydrocyclopenta[5',6']pyrido[3',2':4,5]thieno[3,2-*d*]-[1,3,2]diazaphosphorin-4(1*H*)-one, 1:1 Complex with Pyridine (2a). Obtained from the thienopyridine **1a** (563 mg, 1.88 mmol) and P_4S_{10} (210 mg, 0.47 mmol). Yield 443 mg (50%). Yellow-brown, fine crystalline powder. Mp >250ºC (decomp.). ^{1}H NMR spectrum (500 MHz), δ, ppm (*J*, Hz): 2.08-2.18 (2H, m, CH_2); 2.98-3.12 (4H, m, $2CH_2$); 6.86-6.91 (1H, m, H-4 Fur); 7.03-7.08 (2H, m, H-3 Fur, 1-NH); 7.73 (2H, dd, *J* = 7.5, *J* = 5.0, H-3,5 Py); 8.04-8.10 (1H, m, H-5 Fur); 8.20 (1H, dt, *J* = 7.5, *J* = 1.7, H-4 Py); 8.75 (2H, br. d, *J* = 5.0, H-2,6 Py); 9.97 (1H, d, J_{H-P} = 13.1, 3-NH). Signals for the SH protons were not observed, probably because of deuterium exchange. ^{13}C NMR spectrum, δ, ppm: 23.4 (C-8); 30.8 (C-9); 34.5 (C-7); 108.8 (C Ar); 113.8 (C Ar); 114.8 (C Ar); 127.3 (C-3,5 Py); 130.0 (C Ar); 133.4 (C-4 Py); 138.8 (C Ar); 143.6 (C-2,6 Py); 145.2 (C Ar); 145.6 (C Ar); 147.4 (C Ar); 150.8 (C Ar); 160.4 (C Ar); 161.5 (C Ar); 167.5 (C=O). ^{31}P NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 78.9 (dd, J_{P-H} = 8.9, J_{P-H} = 13.1). Mass spectrum, *m/z*: 394.0 $[M\text{-}Py+H]^+$, 392.0 $[M\text{-}Py\text{-}H]^-$. Found, %: C 51.06; H 3.70; N 11.99. $C_{20}H_{17}N_4O_2PS_3$. Calculated, %: C 50.84; H 3.63; N 11.86.

According to the HPLC-MS data, the purity was 94.5%. The product contained an impurity of the starting compound **1a** (*m/z* 300.2 $[M+H]^+$) and the thionation product **10-(2-furyl)-2-mercapto-2,3,8,9-tetrahydrocyclopenta[5',6']pyrido[3',2':4,5]thieno[3,2-*d*][1,3,2]diazaphosphorine-2,4(1*H*)-dithione (3a)** (1:1 complex with pyridine) (*m/z* 410.0 $[M\text{-}Py+H]^+$, 407.8 $[M\text{-}Py\text{-}H]^-$).

11-[4-Benzyloxy)phenyl]-2-mercapto-2-thioxo-2,3,7,8,9,10-hexahydro[1,3,2]diazaphosphorino-[4',5':4,5]thieno[2,3-*b*]quinolin-4(1*H*)-one, 1:1 Complex with Pyridine (2b). Obtained from the thienopyridine **1b** (421 mg, 1.02 mmol) and P_4S_{10} (113 mg, 0.26 mmol). Yield 213 mg (38%). Yellow crystals. Mp 225-240°C (decomp.). ^{1}H NMR spectrum (500 MHz), δ, ppm (*J*, Hz): 1.66-1.70 (2H, m, CH_2); 1.79-1.84 (2H, m, CH_2); 2.39-2.42 (2H, m, CH_2); 2.98-3.01 (2H, m, CH_2); 5.06 (1H, d, J_{H-P} = 12.6, NH-1); 5.22 (2H, br. s, OCH_2); 7.26 (2H, d, ^3J = 8.7, H Ar); 7.30 (2H, d, ^3J = 8.7, H Ar); 7.36 (1H, t, ^3J = 7.3, H-4 Ph); 7.43 (2H, dd, ^3J = 7.3, ^3J = 7.3, H-3,5 Ph); 7.52 (2H, d, ^3J = 7.3, H-2,6 Ph); 8.00 (2H, dd, *J* = 7.9, *J* = 6.7, H-3,5 Py); 8.52 (1H, t, *J* = 7.9, H-4 Py); 8.89-8.93 (3H, m, 3-NH, H-2,6 Py). Signals for the SH protons were not observed, probably because of deuterium exchange. ^{13}C NMR spectrum, δ, ppm: 22.7, 22.8 (C-8,9); 26.7 (C-10); 33.6 (C-7); 70.1 (OCH_2); 108.4 (C Ar); 115.8 (C Ar); 116.2 (C Ar); 126.4 (C-3,5 Py); 126.6 (C Ar); 128.2 (C Ar); 128.3 (C Ar); 128.4 (2C Ar); 129.0 (C Ar); 130.2 (C Ar); 130.4 (C-4 Py); 137.2 (C Ar); 142.6 (C Ar); 145.6 (C Ar); 145.7 (C-2,6 Py); 157.9 (C Ar); 159.4 (C Ar); 161.2 (C=O). ^{31}P NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 80.1 (dd, $^3J_{P-H}$ = 12.6, $^3J_{P-H}$ = 13.4). Mass spectrum, *m/z*: 524.3 $[M\text{-}Py+H]^+$, 1046.8 $[2M\text{-}2Py+H]^+$. Found, %: C 60.06; H 4.60; N 9.49. $C_{30}H_{27}N_4O_2PS_3$. Calculated, %: C 59.78; H 4.52; N 9.30.

Using a 1.5-fold excess of P_4S_{10} (170 mg, 0.38 mmol) gave a mixture (288 mg), which according to HPLC-MS and ^{1}H NMR spectroscopy contains compounds **2b** and **11-[4-(benzyloxy)phenyl]-2-mercapto-2,3,7,8,9,10-hexahydro[1,3,2]diazaphosphorino[4',5':4,5]thieno[2,3-*b*]quinoline-2,4(1*H*)-dithione (3b)** in

~4:1 ratio. Compound **3b** (as 1:1 complex with pyridine) was identified from the minor peaks in the ^{1}H, ^{13}C, and ^{31}P NMR spectra. ^{1}H NMR spectrum (500 MHz), δ, ppm (*J*, Hz): 5.38 (1H, d, $^3J_{H–P}$ = 13.1, 1-NH); 10.47 (1H, d, $^3J_{H–P}$ = 15.6, 3-NH). ^{13}C NMR spectrum, δ, ppm: 194.6 (C=S). ^{31}P NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 73.7 (dd, $^3J_{P–H}$ = 13.1, $^3J_{P–H}$ = 15.6). Mass spectrum, *m/z*: 540.0 $[M\text{-}Py+H]^+$.

2-Mercapto-7,9-dimethyl-2-thioxo-2,3-dihydropyrido[3',2':4,5]thieno[3,2-*d*][1,3,2]diazaphosphorin-4(1*H*)-one, 1:1 Complex with Pyridine (2d). Obtained from the thienopyridine **1d** (625 mg, 2.82 mmol) and P_4S_{10} (314 mg, 0.71 mmol). Yield 591 mg (53%). Yellow-green, fine crystalline powder. Mp >300°C (decomp.). ^{1}H NMR spectrum (400 MHz), δ, ppm (*J*, Hz): 2.54 (3H, s, CH_3); 2.76 (3H, s, CH_3); 7.13 (1H, s, H-8); 7.53 (2H, ddd, *J* = 7.5, *J* = 5.8, *J* = 1.7, H-3,5 Py); 7.95 (1H, dt, *J* = 7.5, *J* = 1.3, H-4 Py); 8.56 (1H, d, $J_{H–P}$ = 12.1, 1-NH); 8.61 (2H, dd, *J* = 5.8, *J* = 1.3, H-2,6 Py); 10.04 (1H, d, $J_{H–P}$ = 15.8, 3-NH). Signals for the SH protons were not observed, probably because of deuterium exchange. ^{31}P NMR spectrum (D_2O), δ, ppm (*J*, Hz): 79.7 (dd, $J_{P–H}$ = 11.1, $J_{P–H}$ = 15.8). Mass spectrum, *m/z*: 316.0 $[M\text{-}Py+H]^+$, 631.0 $[2M\text{-}2Py+H]^+$, 945.8 $[3M\text{-}3Py+H]^+$. Found, %: C 45.96; H 3.80; N 14.48. $C_{15}H_{15}N_4OPS_3$. Calculated, %: C 45.67; H 3.83; N 14.20.

The use of 2.0 equivalents of P_4S_{10} (625 mg, 1.41 mmol) gave a mixture (490 mg), which according to HPLC-MS and ^{1}H NMR spectroscopy consisted of compound **2d** and **2-mercapto-7,9-dimethyl-2,3-dihydropyrido[3',2':4,5]thieno[3,2-*d*][1,3,2]diazaphosphorine-2,4(1*H*)-dithione (3d)** in a ~6:1 ratio. Compound **3d** (as a 1:1 pyridine complex) was identified from the minor peaks. ^{1}H NMR spectrum (400 MHz), δ, ppm (*J*, Hz): 2.73 (3H, s, CH_3); 7.11 (1H, s, H-8); 8.15 (1H, br. pseudo-s, 1-NH); 11.10 (1H, br. pseudo-s, 3 NH). Mass spectrum, *m/z*: 332.0 $[M\text{-}Py+H]^+$, 665.3 $[2M\text{-}2Py+H]^+$.

2-Mercapto-2,3,7,8,9,10-hexahydro[1,3,2]diazaphosphorino[4',5':4,5]thieno[2,3-*b*]quinoline-2,4(1*H*)-dithione, 1:1 Complex with Pyridine (3c). Obtained from the thienopyridine **1c** (340 mg, 1.38 mmol) and P_4S_{10} (611 mg, 1.38 mmol). Yield 455 mg (79%). Dark-yellow, fine crystalline powder. Mp >250°C (decomp.). ^{1}H NMR spectrum (500 MHz), δ, ppm (*J*, Hz): 1.78-1.94 (4H, m, 8,9-CH_2); 2.86-2.98 (4H, m, 7,10-CH_2); 7.39-7.50 (3H, m, H-11, H-3,5 Py); 7.87 (1H, t, ^3J = 8.3, H-4 Py); 8.23 (1H, d, $J_{H–P}$ = 13.2, 1-NH); 8.61 (2H, br. d, H-2,6 Py). Signals for the SH and 3-NH protons were not observed, probably because of deuterium exchange. ^{13}C NMR spectrum, δ, ppm: 22.7, 22.8 (C-8,9); 28.8 (C-10); 30.1 (C-7); 125.2 (C-3,5 Py); 126.0 (C Ar); 129.3 (C Ar); 132.5 (C Ar); 134.8 (C Ar); 137.4 (C Ar); 138.9 (C-4 Py); 148.3 (C-2,6 Py); 151.4 (C Ar); 159.8 (C Ar); 215.6 (C=S). ^{31}P NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 73.7 (dd, $J_{P–H}$ = 13.2, $J_{P–H}$ = 15.6). Mass spectrum, *m/z*: 358.0 $[M\text{-}Py+H]^+$, 356.0 $[M\text{-}Py\text{-}H]^-$. Found, %: C 47.03; H 4.01; N 12.98. $C_{17}H_{17}N_4PS_4$. (M 436.58). Calculated, %: C 46.77; H 3.92; N 12.83.

According to HPLC-MS data, the purity of the obtained compound **3c** was ~96%. The product contained an impurity (~4%) of the **2-mercapto-2-thioxo-2,3,7,8,9,10-hexahydro[1,3,2]diazaphosphorino-[4',5':4,5]thieno[2,3-*b*]quinolin-4(1*H*)-one (2c)** (1:1 complex with pyridine**)**. Mass spectrum, *m/z*: 342.0 $[M\text{-}Py+H]^+$, 339.8 $[M\text{-}Py\text{-}H]^+$.

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