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Phosphorylthioacetamides in the synthesis of annulated quinoxalines

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Diethoxyphosphorylthioacetamide in the reaction with 2,3-dichloroquinoxaline acted as a thionating reagent, giving diethoxyphosphorylacetonitrile and 2-chloro-3-[(3-chloro-2-quinoxalinyl)thio]quinoxaline. Reactions of phosphorylthioacetamides with *N*-methylquinoxalinium iodide in alcohol media in the presence of a base proceeded stereoselectively to afford *cis*-3-phosphoryl-1,3,3a,4,9,9a-hexahydro-2*H*-pyrrolo[2,3-*b*]quinoxaline-2-thiones.

Key words: phosphorylthioacetamides, 2,3-dichloroquinoxaline, *N*-methylquinoxalinium iodide, annulation, 1,3,3a,4,9,9a-hexahydro-2*H*-pyrrolo[2,3-*b*]quinoxaline-2-thiones.

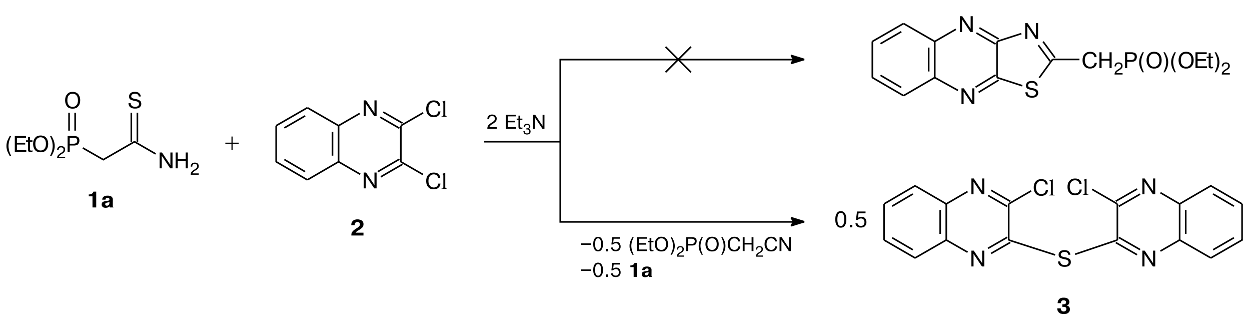
Thioamides of carboxylic acids are widely employed as key precursors for the synthesis of various five- and six-membered heterocycles.[1] In particular, azines containing two and more heteroatoms are known to undergo annulation in the presence of thioamides of carboxylic acids (and some other bisnucleophilic reagents). This ability of azines is behind convenient routes to complex fused heterocyclic systems that are of particular interest from the viewpoint of biological activity.[2—4]

However, publications devoted to the reactivities of phosphorylthioacetamides are scarce.[5—8] To the best of our knowledge, they are mainly concerned with (1) alkylation reactions that occur at the sulfur atom[5,6] and subsequently afford biologically active amidines, (2) the Hantzsch synthesis of phosphorus-containing thiazoles,[7] and (3) regioselective condensation with dimethyl acetylenedicarboxylate yielding phosphorus-containing thiazolidin-4-ones.[8] Limited data on the chemical properties of compounds of this class are largely due to the lack of convenient methods for their preparation.

A recently developed, convenient method for the synthesis of phosphorylthioacetamides with various types of the surrounding of the P atom made these organophosphorus compounds easily accessible.[9] Here we present data on their application as annulating agents in reactions with azines. Diethoxy- and diphenylphosphorylthioacetamides **1a,b** were chosen as the starting organophosphorus substrates and easily accessible 2,3-dichloroquinoxaline and *N*-methylquinoxalinium iodide, as azine components.

Condensation of thioamides $RC(S)NH_2$ (R = H, Me, and Ph) with 2,3-dichloroquinoxaline has been reported[10—12] to give 2-substituted thiazolo[4,5-*b*]quinoxalines, although the physicochemical constants of the resulting 2-methyl derivative do not coincide (the melting points of the samples differ by more than 200 °C). Surprisingly, thioamide **1a** in a reaction with 2,3-dichloroquinoxaline **2** acted as a thionating agent. As a result of the reaction of equimolar amounts of the reactants in ethanol in the presence of triethylamine as an acceptor of HCl, 2-chloro-3-(3-chloroquinoxalin-2-ylthio)quinoxaline **3**, the starting thioamide **1a**, and diethoxyphosphorylacetonitrile were isolated instead of the expected thiazolo[4,5-*b*]quinoxaline (Scheme 1).

Scheme 1



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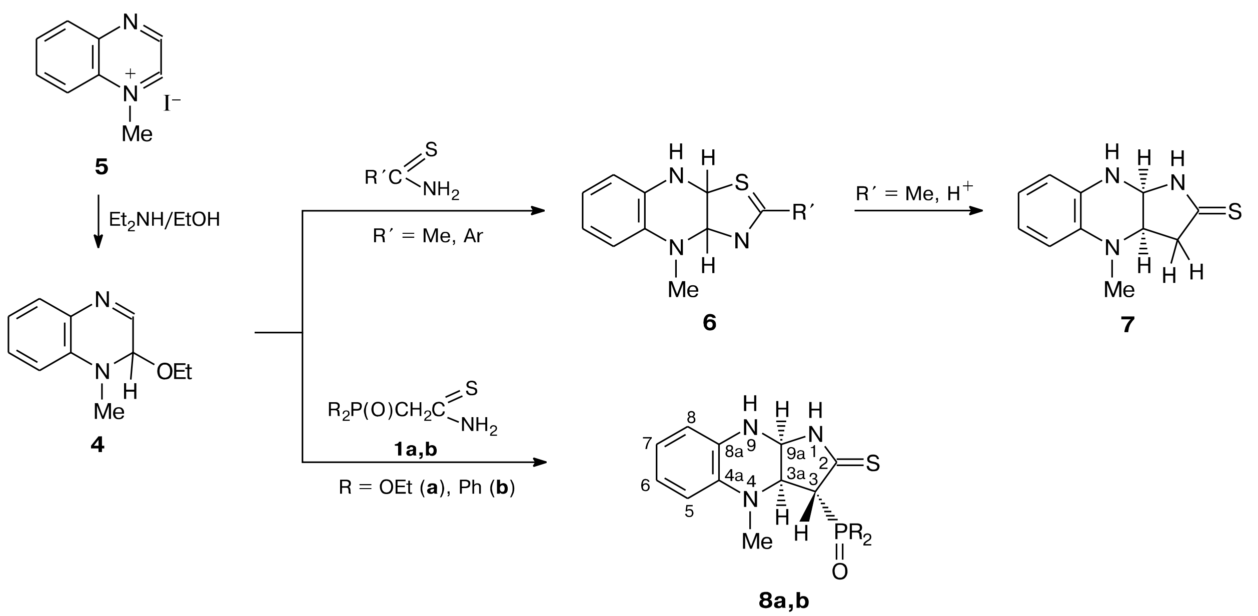
Scheme 2



The structures of all the products of the above reaction were proved by spectroscopic data and confirmed (for compound **1a** and the corresponding nitrile) by TLC with authentic samples. For heterocyclic sulfide **3**, ^{13}C NMR spectroscopy was most informative. The spectrum shows three sets of signals: the signals at δ 128.27, 128.70, 130.65, and 131.14 for the tertiary C atoms of the aromatic ring, the signals at δ 140.68 and 141.23 for the bridgehead C atoms shared by the diazine and benzene rings, and the signals at δ 147.49 and 150.67 for the C atoms bound to the Cl and S atoms, respectively. The mass spectrum (EI, 70 eV) of sulfide **3** contains no molecular ion peak. The most intense peaks relate to the ions $[M - Cl]^{\cdot +}$ and $[M - 2\,Cl]^{\cdot +}$ and fragments arising from the cleavage of the C—S bond. In all the cases, additional peaks appear for ions with the Cl, S, and N atoms due to the isotopic compositions of these elements, the peak intensities corresponding to the natural abundance of the isotopes.

Reactions of carbothioamides with *N*-methyldihydroquinoxaline **4** formed *in situ* from methylquinoxalinium iodide **5** under the action of bases are a convenient route to hydrogenated thiazolo[4,5-*b*]quinoxalines.[13,14] In the case of thioacetamide, thiazoles **6** underwent acid-catalyzed isomerization to yield the tricyclic thiolactam **7**.[14]

Phosphoryl-containing thioamides **1a,b** also reacted easily with preformed 2-ethoxy-1-methyldihydroquinoxaline **4** in ethanol: for diethoxyphosphorylthioacetamide **1a**, the reaction was completed in 30 min, while its diphenylphosphoryl analog **1b** added to quinoxaline in a longer period of time as it dissolved in ethanol. However, in contrast to non-phosphorus thioacetamides, this reaction gave only 4-methyl-3-phosphoryl-1,3,3a,4,9,9a-hexahydro-2*H*-pyrrolo[2,3-*b*]quinoxaline-2-thiones **8a,b** (Scheme 2). Apparently, the introduction of an electron-withdrawing phosphoryl group into the thioacetamide molecule increases its CH acidity so that the condensation rate of heterocyclic amino acetal at the methylene unit of the thioamide is higher than that of nucleophilic addition of the ambident N,S-fragment.

Spin-spin couplings between the ring H and C atoms in positions 3 and 3a and the P atom, a low-field signal for the C=S group (δ 193.28, $^2J_{P,C}$ = 3.8 Hz), and the positions and integral intensities of the signals in the ^{1}H and ^{13}C NMR spectra allowed unambiguous identification of the compounds obtained as thiolactams **8** rather than alternative structures containing the 2-phosphorylmethylthiazole fragment. As with non-phosphorus hydrogenated bicyclic compounds (*cf.* Ref. 14), the low coupling constant of the protons at the bridgehead C(3a) and C(9a) atoms in the ^{1}H NMR spectrum ($^3J_{H(3a),H(9a)}$ = 6.4 (**8a**) and 6.0 Hz (**8b**)) should indicate, according to the Karplus equation, their *cis*-orientation. The absence of the coupling constant $^3J_{H(3a),H(3)}$ (in this case, according to the Karplus equation, the dihedral angle H(3a)—C—C—H(3) should be about 90°*) and the coupling constant $^3J_{P,H(3a)} \approx 10$ Hz suggest that the P atom is *cis* to these groups. It is also noteworthy that the signal for the H(3) proton in the ^{1}H NMR spectrum of compound **8b** is shifted downfield compared to compound **8a** because of

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* The coupling constant ^3J is known to reach a maximum at a dihedral angle of 180°, show the next maximum for the *cis*-orientation (an angle of 0°), approach zero at a dihedral angle of 90°, and increase in the *gauche* configuration (a dihedral angle from 60° to 120°).

spatial shielding by the bulky diphenylphosphoryl group: $\delta_{H(3)}$ 3.54 (**8a**) and 4.54 (**8b**).

In addition, the IR spectra of both thiolactams **8a,b** contain, along with the absorption bands of the P=O stretching vibrations, bands due to the stretching vibrations of both amino groups: a narrow band of the NH vibrations in the quinoxaline ring (3337 cm^{-1}) and a broadened band of the thioamide NH vibrations in the annulated five-membered ring (3204 cm^{-1}).

Thus, the annulation of quinoxalinium salts with phosphorylthioacetamides gives C,N-adducts only: 3-phosphorylhexahydropyrrolo[2,3-*b*]quinoxaline-2-thiones.

Note that non-phosphorylated acetamides containing such electron-withdrawing substituents as acyl or 4-nitrophenyl groups in the α-position react with *N*-methyldihydroquinoxaline **4** analogously to give *cis*-hexahydropyrrolo[2,3-*b*]quinoxalin-2-ones.[15] To compare the reactivities of phosphorylacetamides and phosphorylthioacetamides, we tried to carry out similar transformations with diethoxyphosphorylacetamide $(EtO)_2P(O)CH_2C(O)NH_2$. However, its CH acidity was insufficient for addition to hydrogenated azine **4**; in this case, no polycondensation occurred and the starting organophosphorus substrate was quantitatively recovered.

Experimental

^1H, ^{13}C, and ^{31}P NMR spectra were recorded on Bruker Avance-300 and Bruker AMX-400 instruments in $CDCl_3$ and DMSO-d_6 with the signals for the deuterated solvent as the internal standard (^1H and ^{13}C) and with 85% H_3PO_4 as the external standard (^{31}P). ^{13}C NMR spectra were recorded in the JMODECHO regime: the signals for the C atoms bearing even and odd numbers of protons have opposite polarities. IR spectra were recorded on a Magna-IR 750 FTIR spectrometer (Nicolet, resolution 2 cm^{-1}, number of scans 128, pellets with KBr). Mass spectra were recorded in the detection mode for positively charged ions on a Finnigan LCQ Advantage tandem mass spectrometer (sensitivity limit 2000 *m/z*).

Thioamides **1a,b**,[9] diethoxyphosphorylacetamide,[16] 2,3-dichloroquinoxaline,[17] and *N*-methylquinoxalinium iodide[18] were prepared according to known procedures. Their physicochemical constants were identical with the literature data.

2-Chloro-3-(3-chloroquinoxalin-2-ylthio)quinoxaline (3). Triethylamine (2.02 g, 2.8 mL, 0.02 mol) and diethoxyphosphorylthioacetamide **1a** (2.11 g, 0.01 mol) were added at 20 °C to a suspension of 2,3-dichloroquinoxaline **2** (1.99 g, 0.01 mol) in anhydrous EtOH (50 mL). The reaction mixture was stirred at ~20 °C for 8 h and the solvent was removed *in vacuo*. The residue was dissolved in chloroform and washed with water and dried over Na_2SO_4. The solvent was removed and the residue was recrystallized from ethyl acetate. The yield of compound **3** was 1.5 g (84%), m.p. 192—194 °C (from ethyl acetate). Found (%): C, 53.31; H, 2.25; Cl, 19.49; N, 15.46. $C_{16}H_8Cl_2N_4S$. Calculated (%): C, 53.50; H, 2.24; Cl, 19.74; N, 15.60. ^{13}C NMR (DMSO-d_6), δ: 128.3, 128.7, 130.6, 131.1 (C_{Ar}—H); 140.7, 141.2 (bridgehead C_{Ar}); 147.5 (C—Cl); 150.7 (C—S). MS (*m/z* (I_{rel} (%)): 325 (40), 324 (20), 323 [M – Cl] (100); 288 [M – 2 Cl] (10); 163 [M – 2 Cl – $C_8H_5N_2$ + H] (15), 102 [C_6H_5 – N=C] (14). Column chromatography of the mother liquor on silica gel with CH_2Cl_2 as an eluent gave diethoxyphosphorylacetonitrile[19] (0.5 g, 90% with respect to quinoxaline **2**) and the starting thioamide **1a** (0.8 g). Their physicochemical constants were identical with the literature data.[9]

Diethyl (4-methyl-2-thioxo-2,3,3a,4,9,9a-hexahydro-1*H*-pyrrolo[2,3-*b*]quinoxalin-3-yl)phosphonate (8a). A solution of diethylamine (1.1 mL, 0.01 mol) in diethyl ether (4 mL) was slowly added dropwise to a stirred suspension of *N*-methylquinoxalinium iodide **5** (1.35 g, 0.005 mol) in dry diethyl ether (15 mL). The mixture was stirred for 30 min. The precipitate of diethylamine hydroiodide was filtered off and the filtrate was concentrated *in vacuo*. The residue was dissolved in EtOH (20 mL) and diethoxyphosphorylthioacetamide **1a** (1.06 g, 0.005 mol) was added. The resulting solution turned dark red. The reaction mixture was stirred for 30 min and the light precipitate that formed was filtered off, washed with hot EtOH, and dried in air for a day. The yield of compound **8a** was 1.10 g (62%), a light yellow solid, m.p. 172—174 °C (decomp.). Found (%): C, 50.68; H, 6.21; N, 11.84. $C_{15}H_{22}N_3O_3PS$. Calculated (%): C, 50.69; H, 6.24; N, 11.82. ^{31}P NMR (DMSO-d_6), δ: 19.89. ^1H NMR ($CDCl_3$—DMSO-d_6 (1 : 1)), δ: 1.26, 1.29 (both t, 6 H, 2 CH_3, $^3J_{H,H}$ = 7.1 Hz); 2.75 (s, 3 H, NCH_3); 3.54 (d, 1 H, H(3), $^2J_{P,H}$ = 24.3 Hz); 4.07—4.18 (m, 4 H, 2 OCH_2); 4.28 (dd, 1 H, H(3a), $^3J_{H,H(9a)}$ = 6.4 Hz, $^3J_{P,H}$ = 10.4 Hz); 5.49 (d, 1 H, H(9a), $^3J_{H,H(3a)}$ = 6.4 Hz); 6.34 (br.s, 1 H, NH); 6.51—6.67 (m, 4 H, H arom.); 10.43 (br.s, 1 H, NHCS). ^{13}C NMR (DMSO-d_6), δ: 16.24 (d, CH_3, $^3J_{P,C}$ = 6.4 Hz); 34.88 (NCH_3); 56.80 (d, C(3), $^1J_{P,C}$ = 130.8 Hz); 62.10 (d, OCH_2, $^2J_{P,C}$ = 6.8 Hz); 63.25 (d, C(9a), $^2J_{P,C}$ = 3.0 Hz); 63.52 (d, OCH_2, $^2J_{P,C}$ = 6.8 Hz); 72.77 (s, C(3a)); 111.45 (C(5)); 111.44 (C(8)); 118.27 (C(6)); 119.80 (C(7)); 131.65 (C(8a)); 135.47 (C(4a)); 193.28 (d, C=S, $^2J_{P,C}$ = 3.8 Hz). IR, ν/cm^{-1}: 3337 (narrow, NH(amine)); 3204 (br, NH(amide)); 1608 (w, Ph); 1511 (NHC=S); 1241 (P=O); 1022 (P—O—C); 764, 608.

3-Diphenylphosphoryl-4-methyl-1,3,3a,4,9,9a-hexahydro-2*H*-pyrrolo[2,3-*b*]quinoxaline-2-thione (8b) was obtained analogously from *N*-methylquinoxalinium iodide (0.79 g, 2.91 mmol) and thioamide **1b** (0.80 g, 2.91 mmol) with the exceptions that after addition of compound **1b**, the reaction mixture was stirred for two days and that filtered product **8b** was washed with EtOH and acetone. The yield of compound **8b** was 1.10 g (90%), a yellow solid, m.p. 220 °C (froth.). Found (%): C, 65.91; H, 5.28; N, 9.94. $C_{23}H_{22}N_3OPS$. Calculated (%): C, 65.85; H, 5.29; N, 10.02. ^{31}P NMR (DMSO-d_6), δ: 29.45. ^1H NMR (DMSO-d_6), δ: 3.37 (s, 3 H, NCH_3); 3.96 (dd, 1 H, H(3a), $^3J_{H,H(9a)}$ = 6.0 Hz, $^3J_{P,H}$ = 9.7 Hz); 4.54 (d, 1 H, H(3), $J_{P,H}$ = 9.7 Hz); 5.53 (dd, 1 H, H(9a), $^3J_{H,H(3a)}$ = 6.0 Hz, $^3J_{H,H(9a)}$ = 4.1 Hz); 6.32 (d, 1 H, H(9), $J_{H,H(9a)}$ = 4.1 Hz); 6.49—6.65 (m, 4 H, H(5)—H(8)); 7.46—8.09 (m, 10 H, H arom.); 10.44 (s, 1 H, NHCS). IR, ν/cm^{-1}: 3419 (narrow, NH(amine)); 3075 (br, NH(amide)); 1603 (w, Ph); 1511 (NHC=S); 1182, 1177 (P=O, two conformers); 727, 706, 596.

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