C-PHOSPHORYLATED 4,5-DIHYDRO-THIAZOLES AS PRODUCTS OF THE REACTION OF ACETALS OF α-THIO-CYANATO-α-PHOSPHORYLACET-ALDEHYDES WITH THIOAMIDES

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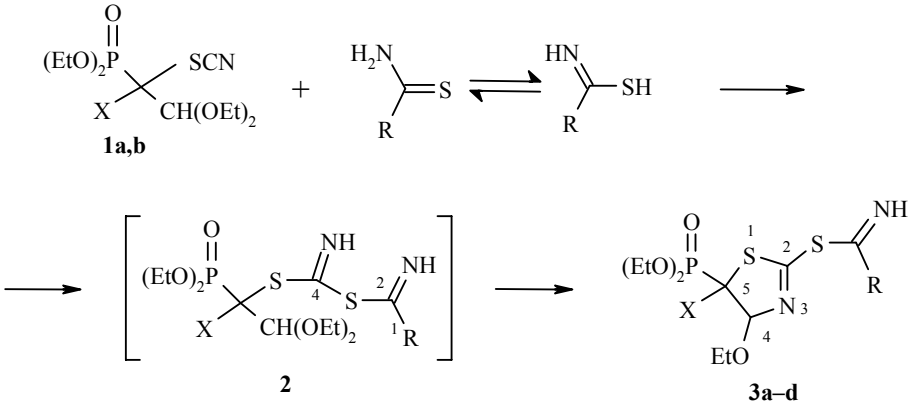
Compounds containing a thiazole ring have a broad spectrum of biological activity such as antimicrobial [1] and anti-inflammatory properties [2]. Thus, it was of interest to use acetals of phosphorylated α-thiocyanatoaldehydes **1** [3] as reagents in condensation with thioamides in order to synthesize thiazole derivatives with various pharmacophoric groups.



2 **3a–d**

1 a X = CO_2Et, **b** X = Ph; **3 a** R = Me, X = CO_2Et; **b** R = Ph, X = CO_2Et; **c** R = Me, X = Ph; **d** R = X = Ph

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We have shown that the reaction of acetals **1** with thioamides in acetonitrile or absolute ethanol gives C-phosphorylated 4,5-dihydro-1,3-thiazoles **3**.

The reaction probably proceeds through formation of linear intermediate **2**. Attack of the proton of the C(4) imino group at the methine carbon atom in intermediate **2** is accompanied by intramolecular cyclization to give heterocycle **3**.

The IR spectra of **3a** and **3b** lack the C(4)=NH absorption band at 2500-2600 cm^{-1} but have bands at 1070 (CH–O), 1290 (P=O), and 1635 (C=N), and 2980 cm^{-1} (C(2)=NH) as well as ketone group stretching bands at 1680-1700 cm^{-1}.

The ^1H NMR spectra of compounds **3a-d** lack signals for the acetal and C(4)=NH imino fragments (at 5.0-5.2 ppm with $^3J_{PH}$ = 2.5 Hz and 6.5-8.0 ppm, respectively). The ratio of the integral intensities of the protons of the ethoxy fragments at the phosphorus atom and at the methine carbon atom (9:2:4) exclude structure **2**. The S–C(R)=NH proton is found in the vicinity of 4.5 ppm as a broad singlet, while the semiaminal proton at C(4) appears as a double doublet (mixture of diastereomers) at 5.1-5.2 ppm with $^3J_{PH}$ = 12.5 Hz. The phenyl ring protons appear as a series of downfield multiplets at 7.2-7.9 ppm. The ^{31}P NMR spectrum shows signals at 15.41 and 16.47 ppm, indicating formation of a mixture of diastereomers.

The IR spectra for KBr pellets were taken on a UR-20 spectrometer. The ^1H NMR spectra were taken for solutions in acetone-d_6 on a Tesla BW-567 spectrometer at 100 MHz with HMDS as the internal standard, while the ^{31}P NMR spectra were taken on a Bruker WP-80 spectrometer at 32.38 MHz with 85% H_3PO_4 as the standard.

5-Diethoxyphosphoryl-4-ethoxy-5-ethoxycarbonyl-2-(1-imino)ethylthio-4,5-dihydrothiazole (3a). A solution of thiocyanatoacetal **1a** (3.83 g, 0.01 mol) and thioacetamide (0.75 g, 0.01 mol) in absolute acetonitrile or ethanol (30 ml) was heated at reflux for 16 h. The solvent was removed in vacuum and 10 ml 3:1 ether–acetone was added to the resultant oil. The yellow crystalline precipitate was filtered off and dried to give 2.31 g (56%) compound **3a**; mp 124-129°C. IR spectrum, ν, cm^{-1}: 1070 (CH–O); 1290 (P=O); 1635 (C=N); 1680 (C=O); 2980 (NH). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.0 (12H, m, $4CH_3$); 2.3 (3H, s, CH_3); 3.5-4.1 (8H, m, $4OCH_2$); 5.1 (1H, d, $^3J_{PH}$ = 12.5, CHO); 7.8 (1H, br. s, NH). ^{31}P NMR spectrum, δ, ppm: 15.41, 16.47. Found,%: N 6.76; P 7.47; S 15.41. $C_{14}H_{25}N_2O_6PS_2$. Calculated, %: N 6.80; P 7.52; S 15.53.

5-Diethoxyphosphoryl-4-ethoxy-5-ethoxycarbonyl-2-iminobenzylthio-4,5-dihydrothiazole (3b) was obtained in 58% yield; mp 136-141°C. IR spectrum, ν, cm^{-1}: 1040 (CH–O); 1290 (P=O); 1635 (C=N); 1590-1595 (Ph); 1700 (C=O); 2990 (NH). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.0 (9H, m, $3CH_3$); 2.35 (3H, s, CH_3); 3.4-4.2 (6H, m, $3OCH_2$); 5.1 (1H, d, $^3J_{PH}$ = 12.5, CHO); 7.2-7.8 (5H, m, C_6H_5); 7.5 (1H, br. s, NH). ^{31}P NMR spectrum, δ, ppm: 15.41, 16.47. Found, %: N 6.56; P 7.67; S 15.46. $C_{17}H_{25}N_2O_4PS_2$. Calculated, %: N 6.73; P 7.45; S 15.38.

5-Diethoxyphosphoryl-4-ethoxy-2-(1-imino)ethylthio-5-phenyl-4,5-dihydrothiazole (3c) was obtained in 70% yield; mp 118-121°C. IR spectrum, ν, cm^{-1}: 1060 (CH–O); 1267 (P=O); 1635 (C=N); 1130 (CH–O); 2979 (NH). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.20 (12H, m, $4CH_3$); 3.2-4.1 (8H, m, $4OCH_2$); 5.1 (1H, d, $^3J_{PH}$ = 12.5, CHO); 7.3-7.9 (5H, m, C_6H_5); 9.2 (1H, br. s, NH). ^{31}P NMR spectrum, δ, ppm: 15.36. Found, %: N 5.76; P 6.38; S 13.44. $C_{19}H_{27}N_2O_6PS_2$. Calculated, %: N 5.91; P 6.54; S 13.50.

5-Diethoxyphosphoryl-4-ethoxy-2-iminobenzylthio-5-phenyl-4,5-dihydrothiazole (3d) was obtained in 75% yield; mp 112.5-114°C. IR spectrum, ν, cm^{-1}: 1080 (CH–O); 1267 (P=O); 1635 (C=N); 1135 (CH–O); 2979 (NH). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.20 (9H, m, $3CH_3$); 3.2-4.1 (6H, m, $3OCH_2$); 5.1 (1H, d, $^3J_{PH}$ = 12.5, CHO); 7.3-7.9 (10H, m, C_6H_5); 8.9 (1H, br. s, NH). ^{31}P NMR spectrum, δ, ppm: 15.33. Found, %: N 5.76; P 6.38; S 13.54. $C_{22}H_{27}N_2O_4PS_2$. Calculated, %: N 5.86; P 6.49; S 13.39.

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