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NEW CONDENSED HETEROCYCLIC SYSTEM WITH A BRIDGEHEAD PHOSPHORUS ATOM

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New condensed heterocyclic system with a bridgehead phosphorus atom has been synthesized by the reaction of imidazolyl anilides of 3,4-dimethoxy- and 3-dimethylaminobenzoic acids with phosphorus(III) halides. The reaction begins with the formation of cyclic halogenophosphonites which are later able to undergo intramolecular heterocyclization to form pentacyclic compounds.

Keywords: phosphorus(III) halides, bridgehead phosphorus atom, condensed heterocyclic systems containing phosphorus, heterocyclization, phosphorylation.

In recent times we have developed new synthetic routes to phosphorus-containing condensed heterocyclic systems, which include direct reactions of functionalized aromatic [1, 2] and heteroaromatic [3-8] compounds with phosphorus(III) halides. We have shown previously that electron-rich substrates [1-6], which react by an addition-elimination mechanism, and 1,3-azoles [7, 8], which react by the so-called ylide mechanism [9], can be used in this method.

Derivatives of 4,5-dihydrobenzo[*e*]imidazo[2,1-*c*][1,4,2]diazaphosphinine **2a,b** have been prepared recently by the phosphorylation of imidazolyl anilide **1a** with phosphorus tribromide and phenylphosphine dibromide [7]. In continuation of this study we have attempted to involve an aryl residue activated by electron donating groups in the heterocyclic aromatic system. It is known, for example, that 3-dimethylaminobenzamides react with phosphorus tribromide and phenylphosphine dibromide to give derivatives of 2,3-dihydro-1H-2,1-benzazaphosphol-3-one [2].

We have discovered that the reaction of the imidazolyl anilide **1b** with phosphorus tribromide in pyridine in the presence of triethylamine gave, as was the case with **1a**, cyclic bromophosphonite **2c**, the phosphorus atom nucleus chemical shift of which was close to that in compound **2a**. The structure of compound **2c** was confirmed by subsequent reactions with morpholine and sulfur and also from the ^{1}H and ^{31}P NMR spectra of compound **3a** containing pentavalent phosphorus atom. The spectroscopic data for the intermediate amidophosphonite and for compound **3a** are comparable with those for the corresponding model compounds [7] (Scheme 1).

The intramolecular heterocyclization of bromophosphonite **2c** into pentacyclic compound appeared to be possible only after prolonged heating in pyridine in the presence of triethylamine. The trivalent phosphorus compound formed (δ ^{31}P 33.0 ppm) was oxidized with elemental sulfur to **4a**. The non-equivalence of the two methoxy groups of the aromatic ring in the ^{1}H NMR spectrum of this compound is one indication of the annelation of the azaphosphole ring.

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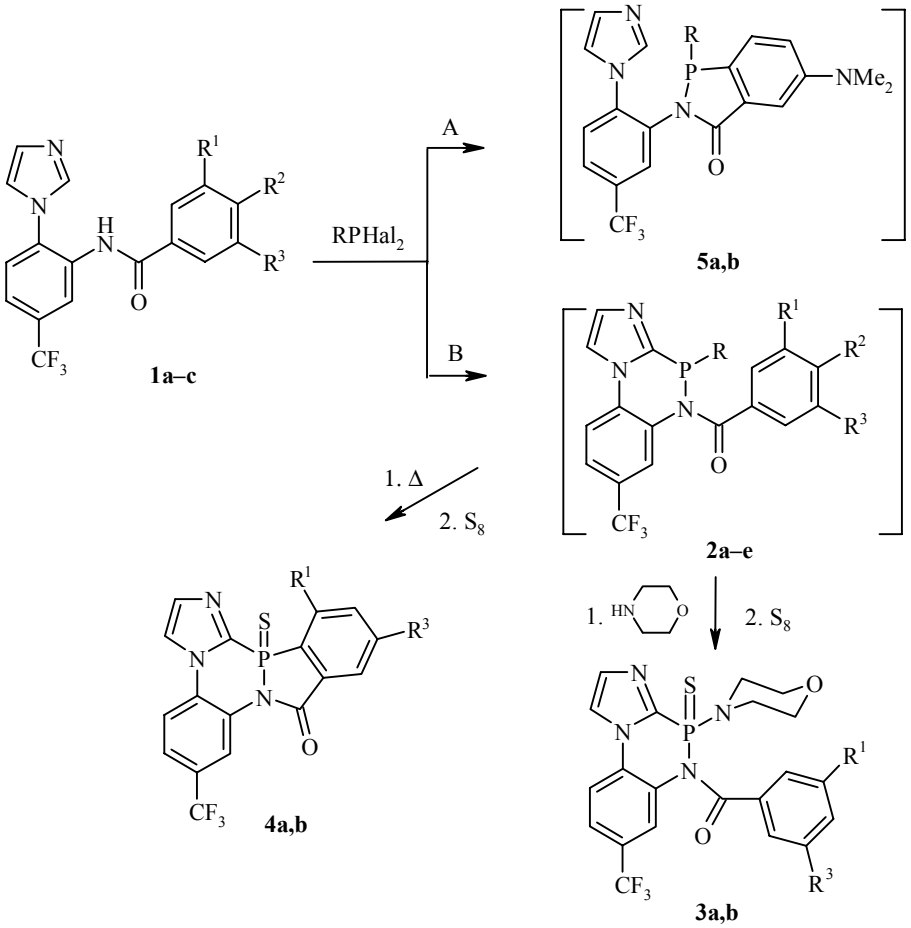
Scheme 1



1 a $R^1 = R^3 = H$, $R^2 = Cl$; **b** $R^1 = R^3 = OMe$, $R^2 = H$; **c** $R^1 = R^2 = H$, $R^3 = NMe_2$;
2 a R = Br, $R^1 = R^3 = H$, $R^2 = Cl$; **b** R = Ph, $R^1 = R^3 = H$, $R^2 = Cl$; **c** R = Br,
$R^1 = R^3 = OMe$, $R^2 = H$; **d** R = Ph, $R^1 = R^2 = H$, $R^3 = NMe_2$; **e** R = Cl, $R^1 = R^2 = H$,
$R^3 = NMe_2$; **3, 4 a** $R^1 = R^3 = OMe$; **b** $R^1 = H$, $R^3 = NMe_2$; **5 a** R = Ph; **b** R = Br

Increase of the electron density in the *ortho* position to the carbamide group of the aromatic ring by using the derivative of 3-dimethylaminobenzoic acid **1c** caused equalization in the reactivity of the imidazole and the electron-rich aromatic groups. In this case the reaction with phosphorus tribromide was ambiguous. In order to estimate quantitatively the reactivity of these two reaction systems (corresponding to heterocyclization by routes **B** and **A**) we carried out the reaction of imidazolyl anilide **1c** with phenylphosphine dibromide.

It was established with the help of ^{31}P NMR spectroscopy [2, 7] that when the reaction was carried out under standard phosphorylation conditions (pyridine/triethylamine) the ratio of the products **2d** and **5a**, corresponding to reaction via routes **B** and **A** respectively, was about 1.0:0.7. Synthesis of the pentacyclic compound **4b** is probably interfered by the ambiguous conversion of bromophosphonite **5b** which is probably connected with the difficulty of realization of the ylide mechanism [9] at intramolecular phosphorylation of the imidazole nucleus.

The reaction of compound **1c** with a highly reactive phosphorylating agent like phosphorus tribromide in the pyridine/triethylamine occurred unselectively and gave an unidentified mixture of products. We considered that heterocyclization of compound **1c** would occur regioselectively under milder conditions. The

expected result was achieved by using phosphorus trichloride in a less polar solvent (dichloromethane) in the presence of triethylamine. The cyclic chlorophosphonite **2e** formed has δ ^{31}P 42.0 ppm in dichloromethane and 50.2 ppm in pyridine which correlates with the values of δ ^{31}P for the brominated analogs **2a** and **2c**. Compound **2e** was converted into the phosphorus(V) compound **3b** by consecutive treatment with morpholine and sulfur. Addition of sulfur was carried out in pyridine solution in the presence of triethylamine on heating according to the previously developed method [7]. Spectroscopic data for both the intermediate amidophosphonite and compound **3b** were in agreement with those for the corresponding model compounds [7].

Since PCl_3, in contrast to PBr_3, did not form cyclic compounds with 3-dimethylaminobenzamides [2], the nucleophilic iodide ion catalysis was used for the intramolecular heterocyclization of compound **2e** in pyridine solution. The phosphorus(III) pentacyclic compound formed had δ ^{31}P 17.9 ppm and, unlike the compound with two methoxy groups, added sulfur relatively rapidly to give the phosphorus(V) compound **4b**.

The derivatives of the new heterocyclic system benzo[3,4][1,2]azaphospholo[1,2-*a*]benzo[*e*]-imidazolo[2,1-*c*][1,4,2]diazaphosphinine, **4a,b**, prepared in this study are high-melting crystalline substances, poorly soluble in the common organic solvents. Compounds **4a,b** hydrolyzed when heated in wet solvents. The possibility of selective hydrolysis of these compounds is the object of a further study.

EXPERIMENTAL

All manipulations of air-sensitive substances were carried out in atmosphere of dry argon. ^{31}P and ^{1}H NMR spectra were recorded with a Varian VXR-300 spectrometer (121 and 300 MHz respectively) with TMS as internal standard (^{1}H) and 85% H_3PO_4 as external standard (^{31}P). IR spectra in KBr disks were recorded with an UR-20 instrument.

The imidazolyl anilide starting materials **1b,c** were synthesized in an analogous way to compound **1a** [7].

1-(3,5-Dimethoxyphenylcarboxamido)-2-(1H-1-imidazolyl)-5-trifluoromethylbenzene (1b). Yield 93%; mp 180°C (toluene–heptane). IR spectrum (KBr), ν, cm^{-1}: 1680 (C=O), 1590. ^{1}H NMR spectrum (DMSO-d6), δ, ppm, *J* (Hz): 3.79 (6H, s CH_3); 6.72 (1H, t, *J* = 2.4, 4-H, ArCO); 6.98 (2H, d, *J* =2.4, 2,6-H ArCO); 7.07 (1H, br.s, imidazole); 7.48 (1H, m, imidazole); 7.74 (1H, d, *J* = 8.4, 3-H); 7.82 (1H, br. s, *J* = 8.4, 4-H); 7.97 (1H, s, imidazole); 8.04 (1H, br. s, 6-H). Found, %: C 57.99, H 3.99, N 11.30. $C_{19}H_{16}F_3N_3O_3$. Calculated, %: C 58.31, H 4.12, N 10.74.

1-(3-Dimethylaminophenylcarboxamido)-2-(1H-1-imidazolyl)-5-trifluoromethylbenzene (1c). Yield 51%; mp 167-168°C (toluene–heptane). IR spectrum (KBr), ν, cm^{-1}: 3300 (N–H), 1650 (C=O), 1590. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm, *J* (Hz): 2.94 (6H, s, NMe_2); 6.92 (1H, dd, *J* = 8.1, 2.4; 6-H ArCO); 7.06 (1H, s, imidazole); 7.08-7.11 (1H, m, 4-H ArCO); 7.11 (1H, s, 2-H ArCO); 7.49 (1H, s, imidazole); 7.73 (1H, d, *J* = 8.4, 3-H); 7.80 (1H, dd, *J* 8.4, 1.8, 4-H); 7.96 (1H, s, imidazole); 8.06 (1H, br. s, 6-H). Found, %: C 61.32; H 4.53; N 14.65. $C_{19}H_{17}F_3N_4O$. Calculated, %: C 60.96; H 4.58; N 14.97.

5-(3,5-Dimethoxybenzoyl)-4-morpholino-4-thioxo-7-trifluoromethyl-4,5-dihydrobenzo[*e*]imidazo-[2,1-*c*][1,4,2]diazaphosphinine (3a). Phosphorus tribromide (0.4 ml, 4.21 mmol) was added to stirred mixture of imidazolyl anilide **1b** (1.65 g, 4.21 mmol) and triethylamine (1.17 ml, 8.40 mmol) in pyridine (20 ml) at -45°C. The reaction mixture was stirred for 2 h in the cold (-45 to 0°C) and then at 20°C for 20 h. The solution of bromophosphonite **2c** formed in this way (^{31}P NMR spectrum, δ: 45.6 ppm) was cooled below 0°C and then triethylamine (0.6 ml, 4.30 mmol) was added with stirring, followed by morpholine (0.37 ml, 4.21 mmol), and then sulfur (160 mg) over 10 min. The reaction mixture was heated for 10 h at 85°C, then cooled to 20°C, diluted with toluene (30 ml), and filtered. The filtrate was evaporated to dryness in vacuum and methanol (4 ml) was added to the residue. The crystalline mass which formed was squeezed out on the filter and washed with a small amount (2-4 ml) of cold methanol. Yield 1.04 g (46%); mp 238-239°C (EtOH–H_2O). IR spectrum (KBr),

ν, cm^{-1}: 3090 (C–H, arom), 2920 (CH_2), 1680 (C=O), 1595. ^{31}P NMR spectrum ($CDCl_3$), δ: 43.9 ppm. ^1H NMR spectrum ($CDCl_3$), δ, ppm, *J* (Hz): 2.84 (2H, m, NCH_2); 3.42 (2H, m, NCH_2); 3.67 (2H, m, OCH_2); 3.8 (8H, s + m, $2OCH_3$ + OCH_2); 6.45 (1H, t, *J* = 2.1, 4-H ArCO); 6.92 (2H, br. s, 2-H ArCO); 7.30 (1H, s, 6-H); 7.49 (1H, m, 2-H); 7.55 (1H, d, *J* = 9.0, 8-H); 7.61 (1H, d, *J* = 9.0, 9-H); 7.66 (1H, m, 1-H). Found, %: N 10.45; P 5.73. $C_{23}H_{22}F_3N_4O_4PS$. Calculated, %: N 10.40; P 5.75.

12,14-Dimethoxy-15-thioxo-7-trifluoromethyl-10H-benzo[3,4][1,2]azaphospholo[1,2-*a*]benzo[*e*]-imidazo[2,1-*c*][1,4,2]diazaphosphinin-10-one (4a). Solution of bromophosphonite **2c** was obtained from imidazoyl anilide **1b** (1.65 g, 4.21 mmol) as described above except that triethylamine (2.0 ml, 14.35 mmol) was used. The reaction mixture was heated at 85°C for 20 h to give pentacyclic phosphorus(III) compound (^{31}P NMR spectrum, δ: 33.0 ppm). Sulfur (150 mg) was added to the reaction mixture which was heated for 5 h at 85°C. The reaction mixture was cooled to 20°C, diluted with toluene (30 ml), and left to crystallize for 12 h. The solid was filtered off, washed initially with benzene, and then with water and ethanol. Yield 0.61 g (32%); mp >300°C. IR spectrum (KBr), ν, cm^{-1}: 1725 (C=O), 1600. ^{31}P NMR spectrum (DMSO-d_6), δ: 28.5 ppm. ^1H NMR spectrum (DMSO-d_6), δ, ppm, *J* (Hz): 3.97 (3H, s, OCH_3); 4.10 (3H, s, OCH_3); 7.13 (2H, m, 11-H + 13-H); 7.46 (1H, s, 2-H); 8.03 (1H, d, *J* = 8.7, 6-H); 8.29-8.30 (2H, m, 5-H + 8-H); 8.40 (1H, s 3-H). Found, %: N 9.46; P 6.72. $C_{19}H_{13}F_3N_3O_3PS$. Calculated, %: N 9.31; P 6.86.

Phosphorylation of Imidazolyl Anilide 1c with Phenylphosphine Dibromide. Phenylphosphine dibromide (0.45 ml, 3.15 mmol) was added with stirring at -30°C to solution of imidazolyl anilide **1c** (1.18 g, 3.15 mmol), triethylamine (0.88 ml, 6.30 mmol), and pyridine (15 ml). The mixture was stirred in cold (-30°C to 0°C) and then for 20 h at 20°C. ^{31}P NMR spectrum, δ: 4.7 ppm (**2d**); 50.0 ppm (**5**).

5-(3-Dimethylaminobenzoyl)-4-morpholino-4-thioxo-7-trifluoromethyl-4,5-dihydrobenzo[*e*]imidazo-[2,1-*c*][1,4,2]diazaphosphinine (3b). Phosphorus trichloride (0.3 ml, 3.43 mmol) was added with stirring at -15°C to mixture of imidazolyl anilide **1c** (1.285 g, 3.43 mmol), triethylamine (1.0 ml, 7.17 mmol) and methylene chloride (20 ml). The reaction mixture was stirred for 1 h while cooling from -15 to 5°C and was then stirred for further 20 h at 20°C. After this triethylamine (0.5 ml, 3.59 mmol) and morpholine (0.3 ml, 3.44 mmol) were added with stirring to the solution of chlorophosphonite **2e** formed (^{31}P NMR spectrum, δ: 42.0 ppm) at 0°C. The reaction mixture was stirred at 20°C for 30 min and then evaporated to dryness in vacuum. Sulfur (130 mg), pyridine (12 ml), and triethylamine (0.2 ml) were added to residue, the mixture was heated at 85°C for 16 h, cooled to 20°C, diluted with toluene (30 ml), and filtered. The filtrate was evaporated to dryness at lowered pressure and the residue was dissolved in toluene (40 ml). The solution was extracted with 10% HCl (50 ml), and the extracted salt was treated with activated charcoal and filtered after 30 min. The base was obtained by treating the filtrate with aqueous ammonia. The solid was filtered off, washed with water, and dried. Methanol (3-4 ml) was added to the obtained yellow powder. The crystalline mass formed was squeezed out on the filter and washed with a small amount of cold aqueous methanol (2-4 ml, MeOH–H_2O, 9:1) to give compound **3b** (510 mg, 29%); mp 165-167°C (EtOH–H_2O, 3:2). IR spectrum (KBr), ν, cm^{-1}: 3090 (C–H arom); 2920, 2870 (CH_2); 1680 (C=O); 1595. ^{31}P NMR spectrum ($CDCl_3$), δ: 43.9 ppm. ^1H NMR spectrum ($CDCl_3$), δ, ppm, *J* (Hz): 2.83 (2H, m, NCH_2); 3.41 (2H, m, NCH_2); 3.65 (2H, m, OCH_2) 3.78 (2H, m, OCH_2); 6.8-6.9 ((2H, dd or d + d, 4,6-H ArCO); 7.19 (1H, dd, *J* = 7.8, 7.8, 5-H ArCO); 7.26 (1H, br. s, 2-H ArCO + $CHCl_3$); 7.31 (1H, br. s, 6-H ArCO); 7.49 (1H, m, 2-H); 7.52 (1H, br. d, *J* = 9.0, 8-H); 7.59 (1H, d, *J* = 9.0, 9-H); 7.66 (1H, m, 1-H). Found, %: N 13.38; P 5.71. $C_{23}H_{23}F_3N_5O_2PS$. Calculated, %: N 13.43; P 5.94.

12-Dimethylamino-15-thioxo-7-trifluoromethyl-10H-benzo[3,4][1,2]azaphospholo[1,2-*a*]benzo[*e*]-imidazo[1,2-*c*][1,4,2]diazaphosphinin-10-one (4b). Solution of chlorophosphonite **2e** was prepared as described above, starting from imidazolyl anilide **1c** (1.715 g, 4.58 mmol). The reaction mixture was evaporated in vacuum. KI (50 mg, calcined for 1 h at 205-210°C) was added to the residue, pyridine (20 ml) and triethylamine (0.65 ml, 4.66 mmol) were poured in and the reaction mixture was heated for 5 h at 85°C. Sulfur (170 mg) was added and the mixture was heated for a further 3 h. The reaction mixture was cooled to 20°C and diluted to twice the volume with toluene. The precipitate was filtered off, washed initially with toluene and then

with water and ethanol. Yield 700 mg (35%); mp > 300°C. IR spectrum (KBr), ν, cm^{-1}: 1720 (C=O), 1595. ^{31}P NMR spectrum (CF_3CO_2D), δ: 16.4 ppm (d, J = 12.7 Hz). ^{1}H NMR spectrum (CF_3CO_2D), δ, ppm, J (Hz): 3.60 (6H, s, $N(CH_3)_2$); 7.88 (1H, s, 11-H); 8.08 (1H, d, J = 8.1, 6-H); 7.46 (1H, s, 2-H). Found, % : N 12.98; P 7.05. $C_{19}H_{14}F_3N_4OPS$. Calculated, %: N 12.90; P 7.13.

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