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Convenient Synthetic Approach to (2-Aryl-5-phenyl-1,3-oxazol-4-yl)phosphonic Acids and Their Functional Derivatives

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Abstract — Successive treatment of available amidophenacylating agents of the general formula PhCOCH·ClNHCOAr with trimethyl phosphite and phosphorus pentachloride gave previously unknown (2-aryl-5-phenyl-1,3-oxazol-4-yl)phosphonic dichlorides which are suitable dtarting materials for preparing other phosphorylated oxazoles containing $P(O)(OH)_2$, $P(O)(NHAlk)_2$, P(O)(OMe)NHAlk, $P(O)(OMe)NAlk_2$, and other groups in the 4 position of the heteroring.

It was previously shown [1–4] that phenylglyoxal (**I**) is easily converted to amidophenacylating agents **II** and **III** that found use in the synthesis of various functionally substituted azoles and azines [4–7]. In the present work we studied the reaction of reagents **III** with trimethyl phosphite, that gave corresponding Arbuzov rearrangement products **IV** and synthesized on their basis a series of novel 4-phosphorylated oxazoles **V**–**XII** (see scheme). The most important proved to be the cyclocondensation of compounds **IV** with excess phosphorus pentachloride, resulting in the synthesis of previously unknown (2-aryl-5-phenyl-1,3-oxazol-4-yl)phosphonic dichlorides **VI** in high yields. The latter exhibited a high reactivity toward various nucleophilic agents, which allowed us to prepare (2-aryl-5-phenyl-1,3-oxazol-4-yl)phosphonic acid hydrates **VII** and other derivatives of these acids **VIII**–**XII**. The structures of all the compounds presented in the scheme were confirmed by their chemical transformations and IR and ^{1}H NMR spectra (Tables 1 and 2).

Compounds **IV** are actually formed by the Arbuzov rearrangement, because they contain a characteristic PCHNH fragment, which follows from the observation in the ^{1}H NMR spectra of a doubled doublet methine proton signal at 6.3–6.4 ppm. At the same time, the involvement of the benzoyl group and amide residue in the cyclizations of **IV** into **V** and **VI** is confirmed by the disappearance of two strong bands at 1690 and 1950 cm^{-1} from the IR spectra. Moreover, the transformation **V** → **VI** is consistent with the disappearance of of the methoxyl proton signal at 3.3–3.4 ppm in the ^{1}H NMR spectrum, whereas in the course of the transformation of **VI** → **XI** the phosphorus atom takes up only one methoxy group that gives a doublet at 3.62 ppm.

Thus, we obtained unambiguous evidence for the structures of phosphorylated oxazoles **V**–**XII**.

It is evident that the scope of application of this synthetic approach to 4-phosphorylated oxazoles is significantly wider than it is presented in the scheme, since, apart from phenylglyoxal, some other aryl- and heterylglyoxals can be involved in such syntheses. From the other side, amidophenacylating agents can be prepared from various aliphatic, aromatic, and heterocyclic carboxamides.

Finally, note that the convenient approach for introducing variously substituted phosphoryl groups in the 4 position of the oxazole ring, developed in the present work, much extends the range of the methods for preparing 4-phosphorylated oxazoles, based on the application of chlorine-containing enamides [8–10].

EXPERIMENTAL

The IR spectra were recorded on a Specord M-80 spectrometer in KBr pellets. The ^{1}H and ^{31}P NMR spectra were recorded on a Varian VXR-400 spectrometer (300 and 121.42 MHz, respectively) in $(CD_3)_2SO$ and $CDCl_3$ solutions against TMS.

Dimethyl (1-acylamino-2-oxo-2-phenylethyl)-phosphonates IVa and IVb. To a solution of 0.01 mol of compound **IIIa** or **IIIb** in 50 ml of benzene, 0.011 mol of trimethyl phosphite was added. The resulting mixture was refluxed for 4 h, cooled,

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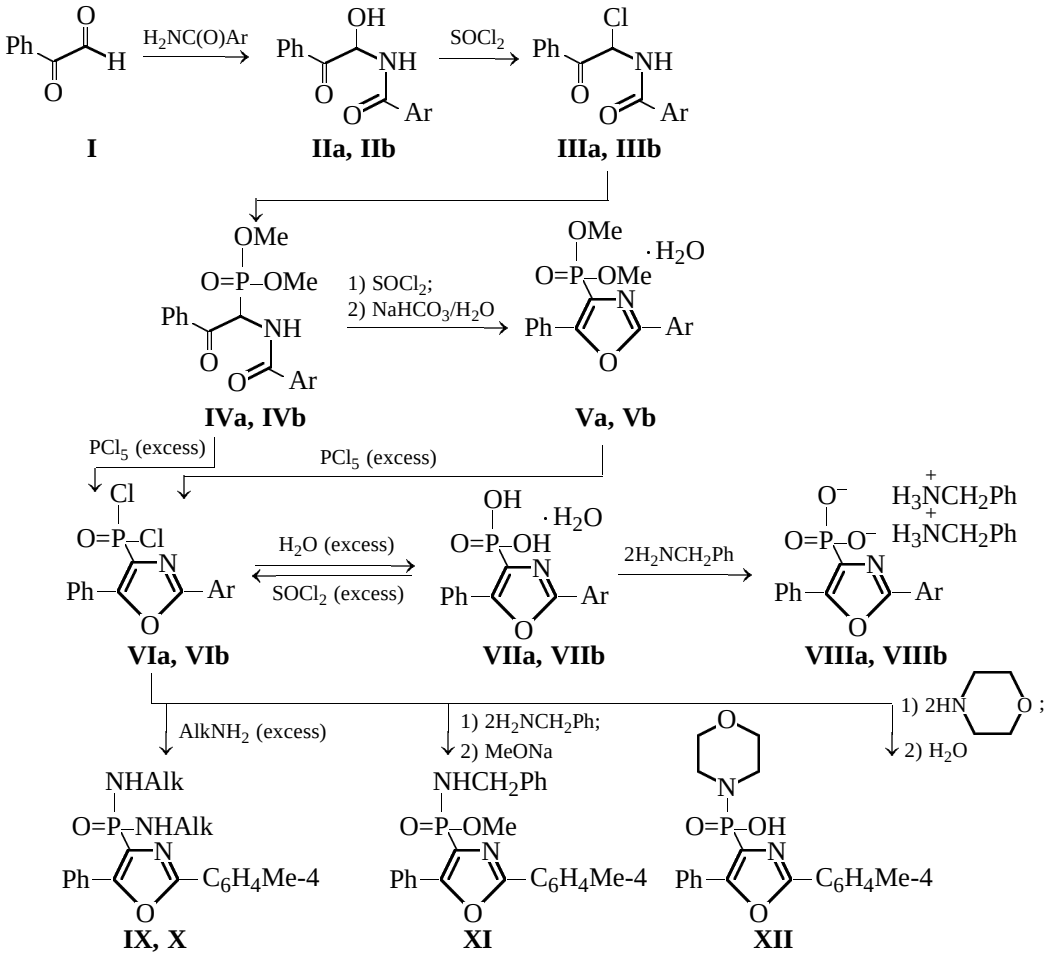

Table 1. ^{1}H and ^{31}P NMR spectra of synthesized compounds

Comp. no.	δ, ppm [$(CD_3)_2SO$]
IVa	3.67 d (3H, CH_3O), 3.69 d (3H, CH_3O), 6.35 d.d (1H, CH, $^{3}J_{HH}$ 9.9, $^{3}J_{HP}$ 23.1 Hz), 7.42–8.02 m (10H, $2C_6H_5$), 9.09 (1H, NH, $^{3}J_{HH}$ 9.9 Hz)
IVb	2.37 s (3H, CH_3), 3.67 d (3H, CH_3O), 3.69 d (3H, CH_3O), 6.34 d.d (1H, CH, $^{3}J_{HH}$ 9.2, $^{3}J_{HP}$ 21.5 Hz), 7.25–7.99 (9H, C_6H_4, C_6H_5), 8.93 d (1H, NH, $^{3}J_{HH}$ 9.2 Hz); δ_P 22.11
Va	3.35 d (3H, CH_3O), 7.36–8.41 m (11H, $2C_6H_5$, OH); δ_P 10.20
Vb	2.39 s (3H, CH_3), 3.35 d (3H, CH_3O), 7.33–8.41 m (10H, C_6H_4, C_6H_5, OH)
VIa[a]	7.53–8.15 m (10H, $2C_6H_5$)
VIb[a]	2.43 s (3H, CH_3), 7.30–8.09 m (9H, C_6H_4, C_6H_5)
VIIb	2.42 s (3H, CH_3), 3.64 d (2H, 2HO), 7.34–8.15 (9H, C_6H_4, C_6H_5); δ_P 6.60
VIIIb	2.38 s (3H, CH_3), 3.84 s (4H, $2CH_2$), 7.23–7.38 m (10H, $2C_6H_5$), 7.89 d, 8.28 d (4H, C_6H_4)
IX	2.56 t (6H, $2CH_3$), 2.40 s (3H, CH_3), 2.90 m (4H, $2CH_2$), 4.51 m (2H, 2NH), 7.38–7.52 m (5H, C_6H_5), 8.07 d, 8.31 d (4H, C_6H_4); δ_P 13.70
X	0.83 t (6H, $2CH_3$), 1.44 q (4H, $2CH_2$), 2.42 (3H, CH_3), 2.78 m (4H, $2CH_2$), 4.34 m (2H, 2NH), 7.31–7.47 m (5H, C_6H_5), 7.97 d, 8.24 d (4H, C_6H_4)
XI	2.42 s (3H, CH_3), 3.62 d (3H, CH_3O), 4.10 m (2H, CH_2), 5.85 m (1H, NH), 7.15–7.50 m (10H, $2C_6H_5$), 7.95 d, 8.17 d (4H, C_6H_4)
XII	2.40 s (3H, CH_3), 3.89 br.s [8H, $N(CH_2)_4O$], 7.30–7.44 m (5H, C_6H_5), 7.92 d, 8.13 d (4H, C_6H_4)

[a] In $CDCl_3$.

Table 2. Constants, yields, and elemental analyses of compounds **IV**–**XII**

Comp. no.	Yield, %	mp, °C (solvent for crystallization)	Found, %		Formula	Calculated, %	
			N (Cl)	P		N (Cl)	P
IVa	76	108–110 (methanol)	4.11	8.63	$C_{17}H_{18}NO_5P$	4.03	8.92
IVb	82	141–143 (methanol)	4.04	8.41	$C_{18}H_{20}NO_5P$	3.88	8.57
Va[a]	73	>340 (benzene)	4.03	9.17	$C_{16}H_{14}NO_4P \cdot H_2O$	4.20	9.29
Vb[b]	69	>340 (benzene)	3.95	8.82	$C_{17}H_{16}NO_4P \cdot H_2O$	4.03	8.92
VIa	72[c]	94–96 (acetonitrile)	(20.05)	9.23	$C_{15}H_{10}Cl_2NO_2P$	(20.97)	9.16
VIb	65[c]	97–99 (acetonitrile)	(19.55)	9.00	$C_{16}H_{12}Cl_2NO_2P$	(20.13)	8.80
VIIa[d]	82	268–270 (acetonitrile)	4.28	9.61	$C_{15}H_{12}NO_4P \cdot H_2O$	4.39	9.70
VIIb[e]	75	180–182 (acetonitrile)	4.05	9.02	$C_{16}H_{14}NO_4P \cdot H_2O$	4.20	9.29
VIIIa	79	171–173[f]	8.06	5.87	$C_{29}H_{30}N_3O_4P$	8.15	6.01
VIIIb	78	189–191[f]	7.88	5.72	$C_{30}H_{32}N_3O_4P$	7.93	5.84
IX	63	151–153 (acetonitrile)	10.98	8.21	$C_{20}H_{24}N_3O_2P$	11.38	8.38
X	76	144–146 (acetonitrile)	10.71	7.57	$C_{22}H_{28}N_3O_2P$	10.57	7.79
XI	64	140–142 (acetonitrile)	6.38	7.13	$C_{25}H_{23}N_2O_3P$	6.51	7.20
XII	57	201–203 (acetonitrile)	7.54	8.38	$C_{20}H_{24}N_2O_4P$	7.65	8.46

[a] Found, %: C 57.45; H 4.82. Calculated, %: C 57.66; H 4.84. [b] Found, %: C 65.56; H 5.15. Calculated, %: C 65.71; H 5.22. [c] By method *a*. [d] Found, %: C 56.26; H 4.32. Calculated, %: C 56.43; H 4.42. [e] Found, %: C 57.39; H 4.59. Calculated, %: C 57.66; H 4.84. [f] After washing with THF.

and treated with 10 ml of hexane. The precipitate was filtered off and recrystallized from methanol.

Hydrogen methyl (2-aryl-5-phenyl-1,3-oxazol-4-yl)phosphonate hydrates Va and Vb. A mixture of 0.005 mol of compound **IVa** or **IVb** and 5 ml of thionyl chloride was refluxed for 2 h. Excess thionyl chloride was removed in a vacuum to leave a viscous oil that was treated with saturated aqueous sodium bicarbonate for crystallization and then recrystallized from benzene.

(2-Aryl-5-phenyl-1,3-oxazol-4-yl)phosphonic dichlorides VIa and VIb. *a*. To a suspension of 0.002 mol of compound **IVa** or **IVb** in 2 ml of phosphorus oxychloride, 0.008 mol of phosphorus pentachloride was added. The resulting mixture was heated for 3 h until gas no longer evolved, and cooled. Excess phosphorus pentachloride was removed by treatment with sulfur dioxide, and volatile compounds were distilled off in a vacuum. The residue was treated with 10 ml of anhydrous acetonitrile for crystallization. The precipitate was filtered off, and compounds **VIa** and **VIb** were used in further transformations without additional purification. Analytically pure samples of compounds **VIa** and **VIb** were obtained by recrystallization from acetonitrile.

b. To a suspension of 0.002 mol of compound **Va** or **Vb** in 15 ml of benzene, 0.005 mol of phosphorus oxychloride was added. The resulting mixture was heated for 2 h at 80°C, cooled, and treated with sulfur dioxide. Volatile compounds were removed in a vacuum. The residue was treated with 10 ml of anhydrous acetonitrile, and the precipitate was filtered off. The yields of compounds **VIa** and **VIb** were 80–90%.

c. A suspension of 0.002 mol of compound **VIIa** (see below) and 0.008 mol of thionyl chloride in 5 ml of benzene was refluxed on an oil bath for 2 h. Volatile compounds were removed in a vacuum, and compound **VIa** was isolated as described above, yield 92%.

(2-Aryl-5-phenyl-1,3-oxazol-4-yl)phosphonic acid hydrates VIIa and VIIb. Compound **VIa** or **VIb**, 0.002 mol, was added in portions with stirring over the course of 1 h to 20 ml of water cooled with ice water. The resulting mixture was left to stand for 24 h at 20–25°C. The precipitate was filtered off and recrystallized from acetonitrile.

Bis(benzylammonium) (2-aryl-5-phenyl-1,3-oxazol-4-yl)phosphonates VIIIa and VIIIb. To a solution of 0.001 mol of acid **VIIa** or **VIIb** in 5 ml of THF, 0.0025 mol of benzylamine was added. The precipitate was filtered off, washed with THF, and dried in a vacuum.

(5-Phenyl-2-*p*-tolyl-1,3-oxazol-4-yl)phosphonic

dialkylamides IX and X. To a solution of 0.002 mol of compound **VIb** in 20 ml of anhydrous dioxane, a solution of 0.005 mol of ethyl- or propylamine in 10 ml of dioxane was added dropwise with stirring and cooling with ice water. The resulting mixture was left to stand for 5 h at 20–25°C. The precipitate was filtered off and recrystallized.

Methyl *N*-benzyl-*P*-(5-phenyl-2-*p*-tolyl-1,3-oxazol-4-yl)phosphonamidate (XI). To a solution of 0.002 mol of compound **VIb** in 20 ml of anhydrous dioxane, a solution of 0.004 mol of benzylamine in 5 ml of anhydrous dioxane was added dropwise with stirring and cooling with ice water over the course of 1 h. The resulting mixture was stirred for 1 h, a solution of 0.001 mol of sodium methylate in 5 ml of methanol was added, and the mixture was stirred for 12 h. The precipitate was filtered off, the solvents were removed in a vacuum, and compound **XI** was recrystallized.

(5-Phenyl-2-*p*-tolyl-1,3-oxazol-4-yl)-phosphonic morpholide (XII). To a solution of 0.002 mol of compound **VIb** in 20 ml of anhydrous dioxane, a solution of 0.004 mol of morpholine in 5 ml of anhydrous dioxane was added dropwise with stirring and cooling with ice water. The resulting mixture was stirred for 4 h, diluted with 5 ml of water, and left to stand for 12 h at 20–25°C. The solvent was removed in a vacuum, and compound **XII** was recrystallized.

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