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Synthesis of C-Phosphorylated Benzenesulfonyl-containing Acetamidines

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Abstract—Reactions of sodium derivatives of C-phosphorylated acetamidines with benzenesulfonyl chloride were studied. The reactions proceed selectively to form benzenesulfonyl-containing acetamidine derivatives. A convenient method for the synthesis of a new type of C-phosphorylated acetamidines was developed utilizing CH-acid properties.

Keywords: CH-acids, organophosphorus compounds, C-phosphorylated amidines, benzenesulfonyl chloride

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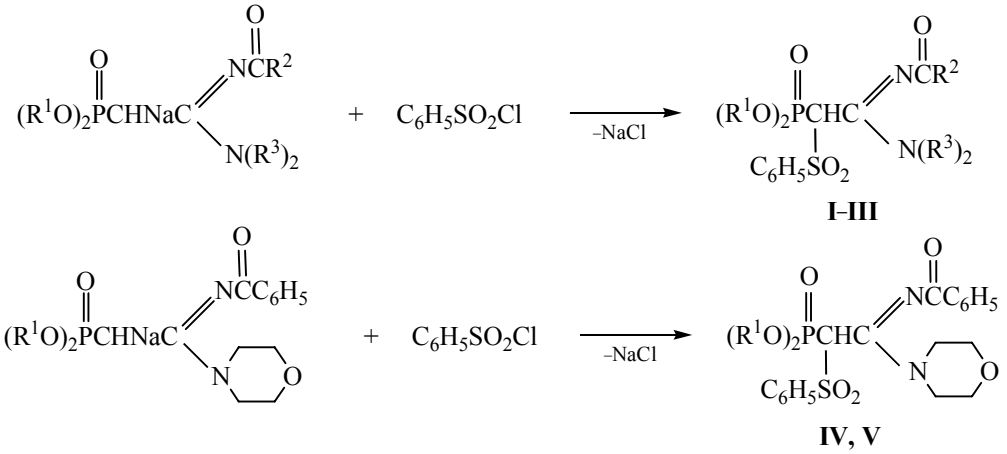
A large number of organophosphorus compounds used as insecticides, plasticizers, and pharmaceuticals are known [1]. Many scientists actively study the relationship between biological activity and chemical structure of organophosphorus compounds [2].

In this work we continued research on acetamidine reactions involving CH-acid properties of the activated methylene group [3, 4]. Aiming to synthesize new amidines exhibiting a high potential biological activity, we performed benzenesulfonylation of sodium derivatives of C-phosphorylated acetamidines with benzenesulfonyl chloride.

Reaction of sodium derivatives of C-phosphorylated acetamidines with benzenesulfonyl chloride resulted in benzenesulfonyl-substituted acetamidines (Scheme 1).

Sodium derivatives of C-phosphorylated acetamidines were prepared according to [5]. Acetamidines containing the least toxic butoxy and isopropoxy groups at the phosphorus atom as well as a benzoyl-

Scheme 1.



R^1 = *i*-C_3H_7, C_4H_9; R^2 = CH_3, C_6H_5; R^3 = C_2H_5, C_3H_7, C_4H_9.

Table 1. Physicochemical properties of C-phosphorylated acetamidines **I–V**

Comp. no.	R^1	R^2	R^3	Yield, %	n_D^{20}	d_4^{20}	MR_D^{20}		Found, %		Formula	Calculated, %	
							found	calculated	N	P		N	P
I	C_4H_9	C_6H_5	C_3H_7	87	1.5216	1.1315	156.29	155.75	5.02	5.48	$C_{29}H_{43}N_2O_6PS$	4.84	5.35
II	*i*-C_3H_7	C_6H_5	C_4H_9	85	1.5314	1.1914	155.90	155.54	4.93	5.59	$C_{29}H_{43}N_2O_6PS$	4.84	5.35
III	C_4H_9	CH_3	C_3H_7	89	1.4835	1.1821	135.92	135.08	5.67	6.11	$C_{24}H_{41}N_2O_6PS$	5.42	6.21
IV	*i*-C_3H_7	–	–	86	1.5014	1.1761	136.19	136.86	5.34	5.98	$C_{25}H_{33}N_2O_7PS$	5.22	5.77
V	C_4H_9	–	–	87	1.5023	1.1632	145.56	146.28	5.13	5.26	$C_{27}H_{37}N_2O_7PS$	4.96	5.49

Table 2. The IR spectral parameters (ν, cm^{-1}) of C-phosphorylated acetamidines **I–V**

Comp. no.	C=N	P=O	C=O	P–O–C	C=C	C–S	O=S=O
I	1664	1245	1735	982–1070	1600	748	1140
II	1678	1234	1738	982–1060	1588	745	1142
III	1664	1248	1736	980–1072	–	746	1139
IV	1666	1243	1735	966–1054	1614	754	1145
V	1675	1233	1744	975–1063	1613	750	1146

Table 3. Data on ^1H NMR spectra of C-phosphorylated acetamidines **I–V**

Comp. no.	δ, ppm (*J*, Hz)
I	0.94 t (12H, CH_3, J_{HH} 6), 1.38 m (12H, CH_2, J_{HH} 6), 3.01 d (1H, CHP, J_{HP} 22), 3.28 t (4H, NCH_2, J_{HH} 7), 3.50 m (4H, CH_2OP, J_{HH} 6, J_{HP} 9), 7.35 m (10H, C_6H_5, J_{HH} 6)
II	0.93 t (6H, CH_3, J_{HH} 6), 1.21 d (12H, CH_3, J_{HH} 6), 1.35 m (8H, CH_2, J_{HH} 6), 2.94 d (1H, CHP, J_{HP} 22), 3.11 t (4H, NCH_2, J_{HH} 7), 4.62 m (2H, CHOP, J_{HH} 6, J_{HP} 9), 7.38 m (10H, C_6H_5, J_{HH} 6)
III	0.91 t (12H, CH_3, J_{HH} 6), 1.35 m (12H, CH_2, J_{HH} 6), 2.15 s [3H, $CH_3C(O)$], 2.96 d (1H, CHP, J_{HP} 22), 3.62 t (4H, NCH_2, J_{HP} 7), 3.98 m (4H, CH_2OP, J_{HH} 6, J_{HP} 9), 7.41 m (5H, C_6H_5, J_{HH} 6)
IV	1.23 d (12H, CH_3, J_{HH} 6), 2.95 d (1H, CHP, J_{HH} 22), 3.42 t (4H, NCH_2, J_{HH} 7), 3.64 t (4H, CH_2O, J_{HH} 6), 4.62 m (2H, CHOP, J_{HH} 6, J_{HH} 9), 7.63 m (10H, C_6H_5, J_{HH} 6)
V	0.94 t (6H, CH_3, J_{HH} 6), 1.33 m (8H, CH_2, J_{HH} 6), 2.99 d (1H, CHP, J_{HP} 22), 3.44 t (4H, NCH_2, J_{HH} 7), 3.67 t (4H, CH_2O, J_{HH} 6), 3.81 m (4H, CH_2OP, J_{HH} 6, J_{HP} 9), 7.58 m (10H, C_6H_5, J_{HH} 6)

substituted imino group were used as substrates. These C-phosphorylated acetamidines are most promising for the search of biologically active substances.

Reaction of sodium derivatives of phosphorylated acetamidines with benzenesulfonyl chloride proceeded even at room temperature and at a molar reactant ratio of 1 : 1.02. The reaction rate increased as the temperature was gradually raised to 50–60°C. In these reactions the C-phosphorylated acetamidines differ little from each other by reactivity.

Physicochemical properties of compounds **I–V** are shown in Table 1.

The obtained compounds were purified by column chromatography eluting with a mixture of chloroform–

diethyl ether–hexane (1 : 3 : 1). The individuality of the compounds obtained was monitored by thin-layer chromatography using Silufol plates. The structure and composition were confirmed by ^{1}H NMR and IR spectroscopy, elemental analysis, molecular refraction and cryoscopy data.

The IR spectra of benzenesulfonyl derivatives of C-phosphorylated acetamidines contained characteristic absorption bands of the groups C=N (1664–1678 cm^{-1}), O=P (1234–1248 cm^{-1}) R–O–C (982–1072 cm^{-1}), C=O (1735–1738 cm^{-1}), C–C_{Ar} (1588–1600 cm^{-1}), C–S (745–750 cm^{-1}), SO_2 (1139–1145 cm^{-1}).

In the ^{1}H NMR spectra of the synthesized compounds **I**–**V** there was a doublet of the methine PCH group at 2.94–3.01 ppm indicating that the benzenesulfonylation occurred at the methylene group.

The IR and ^{1}H NMR spectral data are given in Tables 2 and 3.

In summary, we developed a convenient method of the synthesis of new benzenesulfonyl derivatives of the C-phosphorylated acetamidines.

EXPERIMENTAL

***N*^{1},*N*^{1}-Dipropyl-*N*^{2}-benzoyl-(2-benzenesulfonyl-2-dibutoxyphosphoryl)acetamidine (I).** To a solution of 1 g (0.0021 mol) of *N*^{1},*N*^{1}-dipropyl-*N*^{2}-benzoyl(dibutoxyphosphoryl)acetamidine in 4 mL of anhydrous dioxane was added in small portions with stirring at 20–30°C 0.046 g (0.0021 mol) of sodium. The reaction mixture was stirred until complete consumption of sodium. To a solution of acetamidine sodium derivative was added dropwise with stirring at 20–30°C 0.36 g (0.0021 mol) of benzenesulfonyl chloride in 2 mL of dioxane. The molar ratio of *N*^{1},*N*^{1}-dipropyl-*N*^{2}-benzoyl(dibutoxyphosphoryl)acetamidine–sodium–benzesulfonyl chloride was 1 : 1 : 1.01. The temperature of the reaction mixture was raised to 55–60°C, and the stirring was continued for 5 h. Then sodium chloride was filtered off, and the solvent was removed by distillation in a vacuum (15–20 mmHg). The residue was evacuated at 50°C and 2–4 GPa for 1 h. The target product was chromatographed on silica gel eluting with chloroform–diethyl ether–hexane mixture (1 : 3 : 1). Yield 87%, R_f 0.64.

***N*^{1},*N*^{1}-Dibutyl-*N*^{2}-benzoyl-(2-benzenesulfonyl-2-diisopropoxyphosphoryl)acetamidine (II)** was prepared similarly from (2 g, 0.0048 mol) *N*^{1},*N*^{1}-dibutyl-*N*^{2}-benzoyl(diisopropoxyphosphoryl)acetamidine, 0.11 g (0.0048 mol) of sodium, and 0.53 g (0.0052 mol) of benzenesulfonyl chloride. The molar ratio of acetamidine–sodium–benzenesulfonyl chloride was 1 : 1 : 1. Yield 1.6 g (85%).

***N*^{1},*N*^{1}-Dipropyl-*N*^{2}-acetyl-(2-benzenesulfonyl-2-dibutoxyphosphoryl)acetamidine (III)** was prepared similarly from 1.60 g (0.0039 mol) *N*^{1},*N*^{1}-dipropyl-*N*^{2}-acetyl(dibutoxyphosphoryl)acetamidine, 0.09 g (0.0039 mol) of sodium, and 0.42 g (0.0039 mol) of benzenesulfonyl chloride. The molar ratio of acetamidine–sodium–benzenesulfonyl chloride was 1 : 1 : 1. Yield 1.6 g (89%).

***N*^{1}-Morpholino-*N*^{2}-benzoyl-(2-benzenesulfonyl-2-diisopropoxyphosphoryl)acetamidine (IV)** was prepared similarly from 1.40 g (0.0037 mol) of *N*^{1}-morpholino-*N*^{2}-benzoyl(diisopropoxyphosphoryl)acetamidine, 0.084 g (0.0037 mol) of sodium, and 0.42 g (0.0038 mol) of benzenesulfonyl chloride. The molar ratio of acetamidine–sodium–benzenesulfonyl chloride was 1 : 1 : 1.02. Yield 1.5 g (86%).

***N*^{1}-Morpholino-*N*^{2}-benzoyl-(2-benzenesulfonyl-2-dibutoxyphosphoryl)acetamidine (V)** was prepared similarly from 1.70 g (0.0043 mol) of *N*^{1}-morpholino-*N*^{2}-benzoyl(dibutoxyphosphoryl)acetamidine, 0.099 g (0.0043 mol) of sodium, and 0.48 g (0.0046 mol) of benzenesulfonyl chloride. The molar ratio of acetamidine–sodium–benzenesulfonyl chloride was 1 : 1 : 1.02. Yield 1.9 g (87%).

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