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Alkylation of C-Phosphorylated Acetimidates Containing an Activated Methylene Group

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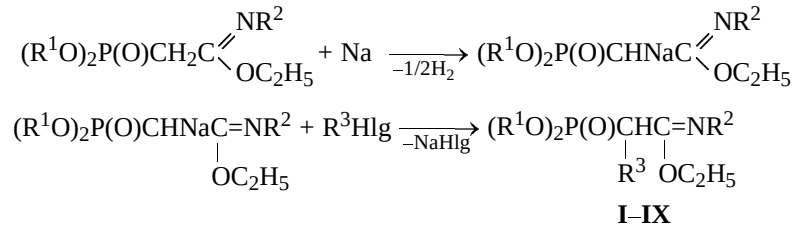
Abstract — In N-substituted dialkoxyphosphorylacetimidates, the methylene group located between the phosphoryl and imide groups exhibits substantial CH acidity. One methylene hydrogen atom is replaced in the reactions of these imidates with sodium metal or sodium alcoholates. The sodium derivatives react with alkyl halides to form the corresponding homologs of N-substituted dialkoxyphosphorylacetimidates.

One of important aspects of the organophosphorus chemistry is the CH acidity of organophosphorus compounds [1, 2]. We have studied C-phosphorylated acetimidates containing an activated methylene group and found that they form sodium derivatives in reactions with sodium metal or sodium alcoholates [3]. With the aim to develop new synthetic routes to organophosphorus compounds and study the CH acidity of the imidates, we performed alkylation of sodium derivatives of C-phosphorylated acetimidates with alkyl halides differing in the electrophilic properties: methyl iodide, ethyl bromide, benzyl chloride, and ethyl chloroacetate. The reactions under the conditions indicated below are selective and yield the corresponding C-alkylation products and sodium halide.



I–IX

For substituents R^1, R^2, and R^3, see table; Hlg = I, Br, Cl.

As substrates we chose imidates containing butoxy and isopropoxy groups at the P atom (the least toxic derivatives) and the acetyl, benzoyl, trimethylsilyl, and dimethoxyphosphoryl substituents at the N atom. Such imidates exhibit various kinds of biological activity [4]. We found that alkylation with CH_3I occurs within 2 h at 30–40°C, whereas alkylation with benzyl chloride requires heating to 60°C for 10 h. This very low reactivity of benzyl chloride in alkylation of the imidates cannot be attributed solely to the inductive effect of the substituent on the reaction center. Apparently, the steric effects of alkylating agents also exert a considerable influence.

Initially the heating is not required, since the reaction starts spontaneously at room temperature. Then, as the sodium derivative is accumulated, it starts to precipitate, and additional heating becomes necessary. Sodium derivatives of the imidates fully dissolve in dioxane on heating to 40–60°C, and, when performed under homogeneous conditions, the subsequent reaction is considerably faster. The reactants were taken in a stoichiometric ratio. The yield of sodium halides in these reactions is almost quantitative. Compounds **I**–**IX** were identified by elemental analysis, from the molecular refraction (see table), and by ^{1}H NMR and IR spectroscopy.

C-Alkylation is a new route to homologs of N-substituted alkyl dialkoxyphosphorylacetimidates, including those containing functional groups. The procedure is simple, does not require isolation of the intermedi-

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N-Substituted ethyl dialkoxyphosphorylacetimidates $(R^1O)_2P(O)CH(R^3)C(=NR^2)OC_2H_5$

Comp. no	R^1	R^2	R^3	Yield, %	n_D^{20}	d_4^{20}	MR_D	
							calculated	found
I	C_4H_9	$CH_3C(O)$	CH_3	80	1.4575	1.0533	86.70	87.22
II	C_4H_9	$C_6H_5C(O)$	CH_3	75	1.4914	1.0880	105.75	106.28
III	*iso*-C_3H_7	$(CH_3O)_2P(O)$	C_2H_5	76	1.4532	1.2116	86.59	87.16
IV	*iso*-C_3H_7	$CH_3C(O)$	C_2H_5	80	1.4498	1.0575	81.51	82.14
V	*iso*-C_3H_7	$(CH_3)_3Si$	C_2H_5	78	1.4579	1.0073	95.06	95.74
VI	*iso*-C_3H_7	$CH_3C(O)$	$CH_2C_6H_5$	82	1.4913	1.0955	101.04	101.63
VII	C_4H_9	$CH_3C(O)$	$CH_2C_6H_5$	73	1.5133	1.1068	111.67	111.35
VIII	C_4H_9	$C_6H_5C(O)$	$CH_2COOC_2H_5$	78	1.5122	1.1576	121.63	121.97
IX	*iso*-C_3H_7	$CH_3C(O)$	$CH_2COOC_2H_5$	80	1.4556	1.0968	93.86	93.19

Comp. no	Found, %		Formula	Calculated, %	
	N	P		N	P
I	4.49	9.13	$C_{15}H_{30}NO_5P$	4.18	9.25
II	3.69	7.61	$C_{20}H_{32}NO_5P$	3.53	7.81
III	3.82	15.68	$C_{14}H_{31}NO_7P_2$	3.62	16.02
IV	4.05	9.33	$C_{14}H_{28}NO_5P$	4.36	9.76
V	4.21	9.33	$C_{15}H_{34}NO_4PSi$	4.30	9.69
VI	3.68	8.12	$C_{19}H_{30}NO_5P$	3.74	8.10
VII	3.28	7.69	$C_{21}H_{34}NO_5P$	3.45	7.52
VIII	3.14	6.43	$C_{23}H_{36}NO_7P$	3.01	6.63
IX	3.41	7.69	$C_{16}H_{30}NO_7P$	3.62	7.94

ate sodium derivative, and provides a high (73–82%) yield of the target compounds.

EXPERIMENTAL

In the experiments, we used a URL-1 universal laboratory refractometer, a Specord M-82 IR spectrometer, and a Tesla BS-487 NMR spectrometer (100 MHz, internal reference HMDS, solvent CCl_4).

The TLC analysis was performed on SiO_2, eluent diethyl ether–acetone, 2 : 1 by volume.

The starting C-phosphorylated N-substituted acetimidates were prepared and described previously [4].

Ethyl *N*-acetyl-2-(dibutoxyphosphoryl)propanimidate I. A 0.34-g portion of Na was added in small portions with vigorous stirring at 20–30°C to a solution of 4.8 g of ethyl *N*-acetyl-2-(dibutoxyphosphoryl)ethanimidate in 15 ml of anhydrous dioxane. Then the reaction mixture was heated to 60°C and stirred for 6 h until the sodium dissolved completely. To the solution of the resulting sodium derivative, 2.2 g of CH_3I was added at 20–30°C with vigorous stirring. The temperature was raised to 40–50°C, and the stirring was continued for 3 h. Then the mixture was cooled to 20°C, the NaI precipitate was filtered off, the solvent was distilled off in a vacuum (15–30 mm Hg), and the residue was kept in a vacuum (2 mm Hg) for 1 h at 50–60°C. Yield of crude ethyl *N*-acetyl-2-(dibutoxyphosphoryl)propanimidate **I** 4 g (80%). The crude product was purified by chromatography on silica gel μLC 5/40, eluent diethyl ether–acetone, 2 : 1 by volume, R_f 0.70. IR spectrum, ν, cm^{-1}: 775, 998–1032 (POC), 1110 (COC), 1270 (P=O), 1660 (C=N), 1672 (NC=O). ^1H NMR spectrum, δ, ppm: 0.77 t (6H, CH_3), 1.08 m (8H, CH_2), 3.96 m (4H, $POCH_2$), 2.95 m (1H, PCH), 1.47 d.d (3H, $PCCH_3$), 3.53 q (2H, OCH_2), 1.08 t (3H, CH_3), 2.06 s [3H, $CH_3C(O)$].

The reaction between 4 g of ethyl *N*-benzoyl-2-(dibutoxyphosphoryl)ethanimidate, 0.24 g of Na, and

1.7 g of CH_3I was performed similarly. Yield of ethyl *N*-benzoyl-2-(dibutoxyphosphoryl)propanimidate **II** 3.1 g (75%), R_f 0.6. IR spectrum, ν, cm^{-1}: 775, 998–1032 (POC), 1110 (COC), 1270 (P=O), 1668 (C=N), 1720 (NC=O), 1600 (C⎓C_{Ar}). ^1H NMR spectrum, δ, ppm: 0.78 t (6H, CH_3), 1.06 m (8H, CH_2), 3.99 m (4H, $POCH_2$), 2.97 m (1H, PCH), 1.44 d.d (3H, $PCCH_3$), 3.51 q (2H, OCH_2), 1.06 t (3H, CH_3), 7.32 m (5H, C_6H_5).

Ethyl *N*-dimethoxyphosphoryl-2-(diisopropoxyphosphoryl)butanimidate III. A solution of 1.51 g of ethyl bromide in 5 ml of anhydrous dioxane was added at 20–30°C with vigorous stirring to a solution of the sodium derivative of ethyl *N*-dimethoxyphosphoryl-2-(diisopropoxyphosphoryl)ethanimidate prepared from 0.32 g of Na and 5 g of ethyl *N*-dimethoxyphosphoryl-2-(diisopropoxyphosphoryl)ethanimidate in dioxane (20 ml). The mixture was heated to 40°C and stirred at this temperature for 4 h. Then the NaBr precipitate was filtered off, and the solvent was distilled off. After keeping in a vacuum (2 mm Hg), 4 g of **III** was obtained, yield 76%. The product was purified by chromatography on silica gel, R_f 0.72. IR spectrum, ν, cm^{-1}: 775, 998–1032 (POC), 1120 (COC), 1260, 1246–1252 (P=O), 1664 (C=N). ^1H NMR spectrum, δ, ppm: 1.23 d (12H, CH_3), 1.26 t (3H, CH_3), 1.82 m (2H, CH_2), 1.24 t (3H, CH_3), 2.89 m (1H, CHP), 4.06 q (2H, OCH_2), 4.61 m (2H, CHOP), 4.61 d [6H, $P(OCH_3)$].

The reaction between 5 g of ethyl *N*-acetyl-2-(diisopropoxyphosphoryl)ethanimidate, 0.4 g of Na, and 1.9 g of ethyl bromide was performed similarly and gave 4.4 g of ethyl *N*-acetyl-2-(diisopropoxyphosphoryl)butanimidate **IV**; yield 80%, R_f 0.68. ^1H NMR spectrum, δ, ppm: 1.26 d (12H, CH_3), 1.29 t (6H, CH_3), 1.88 m (2H, CH_2), 2.06 s [3H, $CH_3C(O)$], 2.87 m (1H, CHP), 4.08 q (2H, OCH_2), 4.63 m (2H, CHOP). IR spectrum, ν, cm^{-1}: 775, 998–1032 (POC), 1120 (COC), 1260 (P=O), 1664 (C=N), 1720 (NC=O).

Ethyl *N*-trimethylsilyl-2-(diisopropoxyphosphoryl)-butanimidate **V** was prepared similarly from 2 g of ethyl *N*-trimethylsilyl-2-(diisopropoxyphosphoryl)ethanimidate, 0.14 g of Na, and 0.66 g of ethyl bromide; yield 1.7 g (78%), R_f 0.78. IR spectrum, ν, cm^{-1}: 760, 845 (SiN), 775, 966–1020 (POC), 1120 (COC), 1260 (P=O), 1666 (C=N). ^1H NMR spectrum, δ, ppm: 0 s (9H, CH_3Si), 1.23 d (12H, CH_3), 1.23 t (3H, CH_3), 1.24 t (3H, CH_3), 1.78 m (2H, CH_2), 2.92 m (1H, CHP), 4.03 q (2H, OCH_2), 4.62 m (2H, CHOP).

Ethyl *N*-acetyl-2-(diisopropoxyphosphoryl)-3-phenylpropanimidate VI. A 0.70-g portion of benzyl chloride was added with stirring to a solution of the sodium derivative of ethyl *N*-acetyl-2-(diisopropoxyphosphoryl)ethanimidate prepared from 0.13 g of Na and 1.6 g of ethyl *N*-acetyl-2-(diisopropoxyphosphoryl)ethanimidate in dioxane. The reaction was exothermic and was accompanied by precipitation of NaCl. The mixture was heated at 60°C for 10 h, after which the NaCl precipitate was filtered off, and the solvent was distilled off from the filtrate. Yield of NaCl 99%. The target product was purified by chromatography on silica gel, R_f 0.62. Yield of **VI** 1.7 g (82%). IR spectrum, ν, cm^{-1}: 775, 998–1032 (POC), 1120 (COC), 1260 (P=O), 1600 (C⎓CAr), 1666 (C=N), 1720 (NC=O). ^1H NMR spectrum, δ, ppm: 1.26 d (12H, CH_3), 1.29 t (3H, CH_3), 2.06 s [3H, $CH_3C(O)$], 2.24 m (2H, CH_2), 2.87 m (1H, CHP), 4.08 q (3H, OCH_2), 4.63 m (2H, CHOP), 7.02 m (5H, C_6H_5).

Ethyl *N*-acetyl-2-(dibutoxyphosphoryl)-3-phenylpropanimidate **VII** was prepared similarly from 5 g of ethyl *N*-acetyl-2-(dibutoxyphosphoryl)ethanimidate, 0.36 g of Na, and 2 g of benzyl chloride; yield 4.7 g (73%), R_f 0.6. IR spectrum, ν, cm^{-1}: 775, 990–1032 (POC), 1120 (COC), 1260 (P=O), 1600 (C⎓C_{Ar}), 1664 (C=N), 1730 (NC=O). ^1H NMR spectrum, δ, ppm: 0.77 t (6H, CH_3), 1.07 m (8H, CH_2), 1.09 t (3H, CH_3), 2.08 s [3H, $CH_3C(O)$], 2.22 m (2H, CH_2), 2.97 m (1H, CHP), 3.58 q (3H, OCH_2), 3.99 m (4H, CH_2OP), 7.12 m (5H, C_6H_5).

Ethyl *N*-benzoyl-2-(dibutoxyphosphoryl)-3-(ethoxycarbonyl)propanimidate VIII. A 0.96-g portion of ethyl chloroacetate was added with stirring to a solution of the sodium derivative of ethyl *N*-benzoyl-2-(dibutoxyphosphoryl)ethanimidate prepared from 0.18 g of Na and 3 g of ethyl *N*-benzoyl-2-(dibutoxyphosphoryl)ethanimidate in dioxane. The reaction was exothermic and was accompanied by precipitation of NaCl. The mixture was heated to 50°C for 3 h, after which the NaCl precipitate was filtered off, and the solvent was distilled off from the filtrate. Yield of NaCl 99%. The target product was purified by chromatography on silica gel, R_f 0.54. Yield of **VIII** 2.8 g (78%). IR spectrum, ν, cm^{-1}: 775, 998–1032 (POC), 1108 (COC), 1266 (P=O), 1668 (C=N), 1672 (NC=O), 1720 (C=O), 1596 (C⎓C_{Ar}). ^1H NMR spectrum, δ, ppm: 0.78 t (6H, CH_3), 1.08 m (8H, CH_2), 4.00 m (4H, $POCH_2$), 3.34 m (1H, PCH), 1.38 d.d [2H, $CH_2C(O)$], 4.24 q (2H, OCH_2), 1.3 t (3H, CH_3), 3.92 q (2H, $COCH_2$), 1.08 t (3H, CH_3), 7.36 m (5H, C_6H_5).

Ethyl *N*-acetyl-2-(diisopropoxyphosphoryl)-3-(ethoxycarbonyl)propanimidate **IX** was prepared similarly from 6 g of ethyl *N*-acetyl-2-(diisopropoxyphosphoryl)ethanimidate, 0.47 g of Na, and 2.5 g of ethyl chloroacetate. Yield 6.2 g (80%), R_f 0.45. IR spec-

trum, ν, cm^{-1}: 775, 998–1032 (POC), 1108 (COC), 1245 (P=O), 1664 (C=N), 1670 (NC=O), 1720 (C=O). ^1H NMR spectrum, δ, ppm: 1.14 t (3H, CH_3), 1.25 d (12H, CH_3), 1.28 t (3H, CH_3), 2.1 s [3H, $CH_3C(O)$], 2.68 d.d (2H, CH_2), 3.11 m (1H, PCH), 4.07 q (4H, OCH_2), 4.62 m (2H, CHOP).

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