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Phosphorylation of 1,3-Di(N-alkyl)Azoles by Phosphorus(V) Acid Chlorides - a Route to Potential Haptens Derived from Phosphinic Acids

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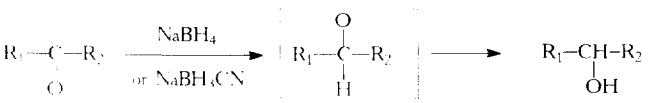
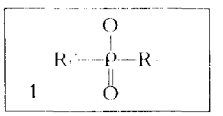
Abstract. Phosphorylation of N-alkylated imidazoles and benzimidazoles at C-2 by CH_3POCl_2, $PhPOCl_2$, $POCl_3$ in pyridine-triethylamine solution is described. The formed heteroaryl-substituted phosphinic or phosphonic acid chlorides were transformed without isolation into the corresponding phosphinic (phosphonic) acids, their salts or amides with moderate yields. This reaction opens a simple way to potential haptens derived from phosphinic acids. These haptens mimic tetrahedral transition state of many reactions and can be used to obtain catalytic antibodies. The functionalized heteroarylsubstituted phosphinic acids which have been used as hapten precursors were obtained by phosphorylation of 1-alkyl-5-nitrobenzimidazole or by usage of a new phosphorylating reagent - (4-trichloromethylphenyl)phosphonic dichloride

Phosphonic acids and their derivatives which mimic tetrahedral transition states of many reactions have been widely used as haptens to elicit catalytic antibodies[1]. Much less attention has been paid to *phosphinic* acid derivatives, though in some cases they seem to be a better choice, resembling the transition state more closely. For example, for reduction of diheteroaromatic ketones by complex borohydrides (scheme 1) it is reasonable to raise catalytic antibodies against diheteroaromatic phosphinate haptens **1**.



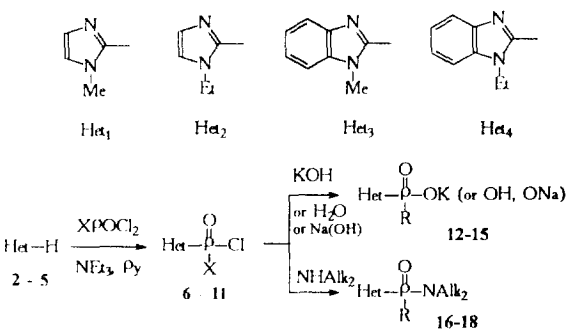


Scheme 1

R_1, R_2 - heterocyclic substituents or Ph. R_1' is R_1 with the "spacer arm"[1]

The simplest synthetic route to the compounds **1** would be the direct C-phosphorylation of heterocycles by phosphorus(V) acid chlorides. To our knowledge, this reaction is not known, although similar C-acylation is quite long-explored[2]. It has also been shown by one of us[3,4] that some nitrogen-containing heterocycles undergo facile phosphorylation by phosphorus(III) acid chlorides. The possibility of a simple approach to haptens **1** stimulated us to investigate in detail the reaction between phosphorus(V) acid chlorides and N-alkylated imidazoles and benzimidazoles **2-5**, as the simplest and the most versatile model heterocycles.

We find that CH_3POCl_2, $PhPOCl_2$, $POCl_3$ react readily in pyridine-triethylamine solutions with 1-methyl (or 1-ethyl) imidazole and benzimidazole to give heteroaryl-substituted phosphonic or phosphinic acid chlorides **6-11**. Substitution proceeds exclusively at the second position of the heterocycles. The highly reactive compounds **6-11** have been characterized by ^{31}P-NMR spectroscopy and transformed into the corresponding phosphinic (phosphonic) acids, their salts or amides **12-18** without isolation (scheme 2).



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3, Het = Het_2
4, Het = Het_3
5, Het = Het_4

6, Het = Het_1, X = Cl
7, Het = Het_1, X = Me
8, Het = Het_2, X = Cl
9, Het = Het_2, X = Ph
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11, Het = Het_4, X=Ph

12, Het = Het_2, R = Ph
13, Het = Het_3, R = Ph
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15, Het = Het_2, R = ONa
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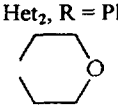
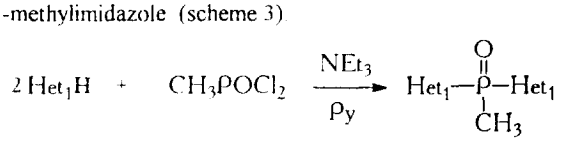
Alk_2 = 

Scheme 2

The reaction rates and yields in the case of $POCl_3$ differ from those of $PhPOCl_2$ and CH_3POCl_2 phosphorylation. It was found by ^{31}P-NMR that $POCl_3$ reacts with **2-5** much more quickly. However, C-phosphorylated products **6, 8** were obtained with low yields even in the presence of a large excess of $POCl_3$. Major by-products in this case are 1,1'-dimethyl(or diethyl)-*1H*,1'H-[2,2']-*bis*-benzimidazolyl (or imidazolyl)[5]. The reaction of Ph_2POCl with **2-5** does not proceed appreciably: in our hands, neither C-phosphorylated products, nor *bis*-azoles have been obtained. Compounds with two heterocyclic substituents are also available: we have obtained di-(1-methyl-*1H*-imidazol-2-yl)methylphosphine oxide **19** using 1 equiv. of phosphorylating reagent per ~2 equiv. of 1-methylimidazole (scheme 3).



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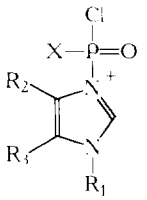
Scheme 3



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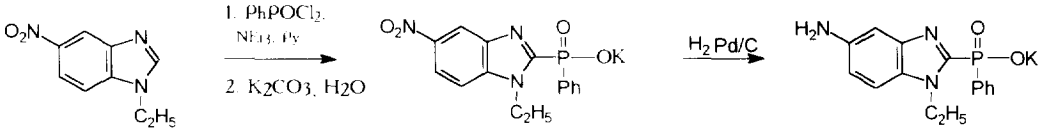
It should be noted that features of the phosphorylation reactions described above, and the by-products, are similar to those for acylation of **2-5** by acid chlorides[5]. Thus, it can be postulated that the mechanisms of these reactions are also similar. The mechanism of the acylation was believed[2] to include the formation of an ylide moiety. In the phosphorylation reaction (I), phosphoryl group transfer in the ylide **20** may give the 2-phosphorylated heterocycles **6-11**, while oxidative dimerization may lead to 2,2'-*bis*-azoles.

To synthesize haptens **1** we had to elaborate the approaches to those hetaroarylphosphinic acid derivatives possessing a functional group in one of the aryl or heteroaryl substituents. This functional group is used to attach the spacer arm which, in turn, is employed to conjugate the haptens to carrier proteins[1]. The most frequently used functional groups for this purpose are amino and carboxyl groups, which allow easy linkage of a hapten and spacing arm *via* amide bond formation. Evidently these groups should be "hidden" at the phosphorylation stage to resist vigorous reaction conditions. The nitro or trichloromethyl group, which can be easily transformed after the phosphorylation into amino or carboxyl functions, respectively, are the most suitable for this purpose. These groups can be introduced either in the starting heterocyclic compound, or in the phosphorylating reagent. All things considered, two approaches to the functionalized phosphinic acid derivatives have been elaborated.

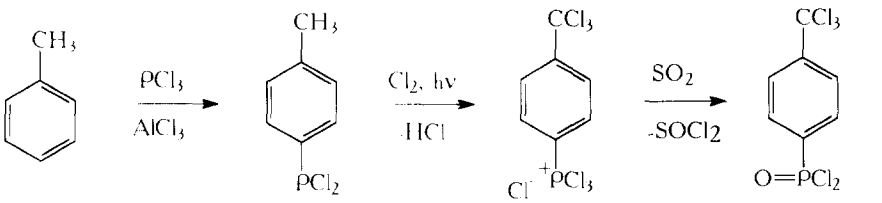
The first involves the phosphorylation of nitrosubstituted 1-alkylbenzimidazoles by $PhPOCl_2$. Hydrolysis of the phosphorylation end product and the nitro group reduction gave a hapten precursor **21** (scheme 4).



22 **21**

Scheme 4

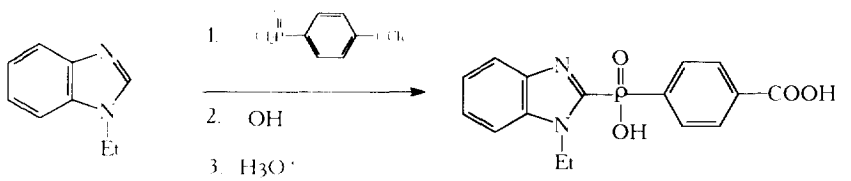
For the second approach, the phosphorylating reagent is required to possess a "hidden" amino or carboxyl group. With this in mind, we have synthesized the new reagent **23** starting from toluene (scheme 5).



24 **23**

Scheme 5

The main side reaction on the way to **23** is nucleophilic substitution in **24** which leads to 1-chloro-4-trichloromethylbenzene. The similar substitution of the phosphorus-containing functional groups in aromatic compounds have been described earlier[6]. Fortunately, the intermediate compound **24** was precipitated from reaction mixture thus avoiding the substitution. Phosphorylation of 1-ethylbenzimidazole by **23** followed by hydrolysis yields a hapten precursor **25** with the carboxyl group in the phenyl substituent (scheme 6).



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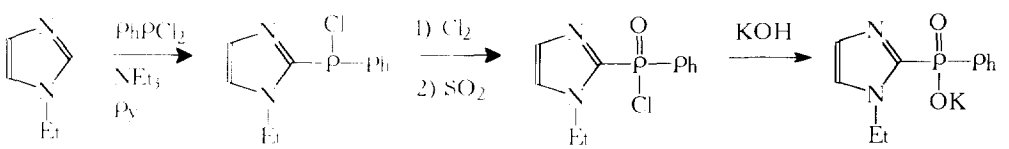
Scheme 6

Monitoring the reaction mixtures by ^{31}P-NMR spectroscopy showed that electron-withdrawing -NO_2 group in the heterocyclic compound causes an appreciable decrease of the phosphorylation reaction rate (see the experimental part) in comparison with the corresponding reaction of the unsubstituted N-ethylbenzimidazole. At the same time, the presence of electron-withdrawing -CCl_3 group in the phosphorylating reagent leads to a faster reaction rate with 1-ethylbenzimidazole, as compared with the analogous reaction of $PhPOCl_2$. The yield of the C-phosphorylated product, however, is larger in the case of the 1-ethyl-5-nitrobenzimidazole, while the phosphorylation by **23** is accompanied (as with $POCl_3$) by formation of 1,1'-diethyl-*1H*,1'H-[2,2']-*bis*-benzimidazolyl.

In principle, heteroarylphosphinic acid derivatives could be obtained using the reaction between **2-5** and phosphorus(III) acid chlorides, followed by hydrolysis and oxidation. We have synthesized compound **12** by this approach (scheme 7), but the yield is about half that in the reaction (I).

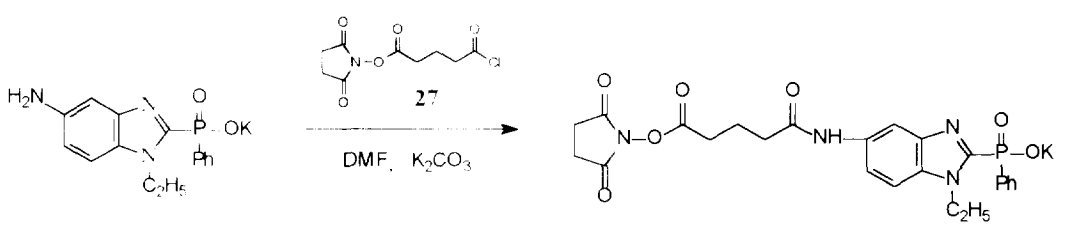


12

Scheme 7

Moreover, it is quite impossible to perform C-phosphorylation of nitro-substituted heterocycles by phosphorus(III) acid chlorides because of oxidation of the phosphorus atom[7]. For the same reason, it seems likely to be problematic to obtain phosphorylating reagents like **23** with trivalent phosphorus.

A hapten **26** which mimics the diheteroaryl ketone reduction (scheme 1) transition state and can be used directly for conjugation with a carrier proteins was synthesized from **21** by the following scheme (scheme 8):



21 **26**

Scheme 8

EXPERIMENTAL

NMR spectra were recorded on a Bruker WP-100SY spectrometer (100,13 MHz for protons), TMS was used as an internal standard for ^{1}H and ^{13}C-NMR spectra, 20% H_3PO_4 was an external standard for ^{31}P-NMR measurements. IR spectra were measured on SP3-300 Pye Unicam infrared spectrophotometer. Melting points were measured on a hot stage and are uncorrected. Pyridine and triethylamine were dried over KOH and distilled. 1-Ethyl-5-nitrtobenzimidazole was prepared by nitration of 1-ethylbenzimidazole as described previously[8]; 5- and 6-substituted derivatives obtained were separated by fractional crystallization from benzene. *p*-Tolylphosphonous dichloride was also prepared by the known procedure[9].

Phosphorylation of 2-5 by $PhPOCl_2$, CH_3POCl_2, $POCl_3$ was performed using the following standard procedure. (All the operations must be carried out under a dry, inert atmosphere.) To a stirred mixture of the starting heterocyclic compound (1 equiv., usually 8 mmol), triethylamine (1.13 equiv. for the reaction of CH_3POCl_2, $PhPOCl_2$, or 3 equiv. for the phosphorylation by $POCl_3$), and pyridine (to give about 1M solution of the heterocyclic compound) the phosphorylating reagent (1 equiv. of CH_3POCl_2 or $PhPOCl_2$, 2.5 equiv. of $POCl_3$) were added dropwise during 10 min. The reaction is slightly exothermic; the formation of crystals (NEt_3·HCl) was observed. The course of the reaction can be easily followed by ^{31}P-NMR spectroscopy. After the integrated intensity of the end product ^{31}P-NMR signal stopped changing relative to all other signals, the reaction mixture was treated with aq. K_2CO_3, KOH, or with dialkylamine as described below.

To compare the rates of **6-11** formation the corresponding starting compounds were mixed carefully in the molar ratio mentioned above directly in calibrated NMR tubes. Dry pyridine-d5 was used as the solvent, the concentration of the starting heterocycles was 1M. ^{31}P-NMR spectra were measured from time to time to follow the process. Relaxation delay was 5 s before each scan.

The compound number, the corresponding approximate phosphorylation reaction time and ^{31}P-NMR data for **6-11** are given below: **6**, <5 min., 2.5; **7**, 8 h, 23; **8**, <5 min., 3.0, **9**, 5 h, 29; **10**, 6 h, 30, **11**, 6 h, 29.

(1-Ethyl-*1H*-imidazol-2-yl)phenylphosphinic acid potassium salt (12) was obtained from 0.68 g of **3** (7.05 mmol). The reaction mixture obtained after the phosphorylation of **3** by $PhPOCl_2$ was poured carefully into 50 ml of 20% K_2CO_3 in H_2O. After refluxing for 0.5 h, the solution was evaporated by half, filtered and then evaporated to dryness *in vacuo*. The product was extracted from the remained solid with dry methanol. Crystallization from wet chloroform yielded **12** (per 5 molecules of H_2O). The crystals were dried *in vacuo* over P_4O_{10}, to obtain **12** as a white powder (1.43 g, 74%). ^{31}P-NMR (D_2O, δ): 6.8 (pH=6); 7.1 (pH=1); 14.1 (pH=9); ^{1}H-NMR ($CDCl_3$:CD_3OD, 3:1, δ): 7.65–7.98 (m, 2H); 7.18-7.50 (m, 3H); 7.02 (dd, $^{3}J_{H-H}$=$^{4}J_{P-H}$=1.5 Hz, 1H); 6.93 (dd, 1H); 4.18 (q, 2H), 1.09 (t, 3H). Anal. Calcd for $C_{11}H_{12}KN_2O_2P$: C, 48.16; H, 4.41. Found: C, 48.05; H, 4.43.

(1-Ethyl-*1H*-benzimidazol-2-yl)phenylphosphinic acid (14). After the phosphorylation of **5** (1.375 g, 7.05 mmol) by $PhPOCl_2$ the reaction mixture was treated with 40 ml 5% aqueous KOH, evaporated to 20 ml, cooled. The precipitate was filtered off. Hydrochloric acid (10%) was added to the filtrate while the pH became ~4. The product was extracted with chloroform (6x50 ml), the combined extracts were evaporated. The remained solid was dried, the product was re-precipitated from methanol with benzene. White powder, m.p. 235°C (1.11 g, 63%). ^{31}P-NMR ($CDCl_3$:CD_3OD, 3:1, δ) 3.5; ^{1}H-NMR ($CDCl_3$:CD_3OD, 3:1, δ): 7.33–8.13 (m, 9H), 4.74 (q, 2H), 1.24 (t, 3H). Anal. Calcd for $C_{15}H_{15}N_2O_2P$: C, 62.93; H, 5.28. Found: C, 62.88; H, 5.31.

(1-Methyl-*1H*-benzimidazol-2-yl)phenylphosphinic acid (13) was prepared analogously from **4** (1 g, 7.6 mmol). White powder, m.p. 229°C, 768 mg (37.1 %). ^{31}P-NMR ($CDCl_3$:CD_3OD, 3:1, δ) 0.0, sodium salt in CD_3OD: 11.0; ^{1}H-NMR ($CDCl_3$:CD_3OD, 3:1, δ): 7.60–8.11 (m, 3H), 7.44-7.55 (m, 6H), 4.16 (s, 3H). Anal. Calcd for $C_{14}H_{13}N_2O_2P$: C, 61.76; H, 4.81. Found: C, 61.72; H, 4.78.

(1-Ethyl-*1H*-imidazol-2-yl)phosphonic acid sodium salt (15) was obtained from **3** (0.68 g, 7.05 mmol). The reaction mixture obtained after the phosphorylation of **3** by $POCl_3$ was poured carefully into 50 ml of 20% Na_2CO_3 in H_2O. After refluxing for 0.5 h, the solution was evaporated by half, filtered, washed with chloroform (3 x 50 ml), and then evaporated to dryness *in vacuo*. The product was extracted from the remained solid with ethanol (100 ml), the ethanol solution was evaporated to ~20 ml. The product formed was filtered, washed with cold ethanol, dried. Pink powder, contains traces of Na_2CO_3, 0.15 g (11.1 %). ^{31}P-NMR (D_2O, δ): -4.0; ^{1}H–NMR (CD_3OD:D_2O, δ): 7.12 (dd, $^3J_{H-H}$=$^4J_{P-H}$=1.2 Hz, 1H); 6.95 (dd, 1H), 4.23 (q, 2H), 1.31 (t, 3H);

(1-Methyl-*1H*-imidazol-2-yl)methylphosphinic acid diethylamide (16). The phosphorylation was carried out with 1-methylimidazole (1.543 g, 18.8 mmol) by CH_3POCl_2. After the reaction at room temperature (8 h) the mixture became dark brown. Diethylamine (2.924 g, 40 mmol) was added to the stirred and cooled in ice bath reaction mixture during 20 min. Pyridine was removed under reduced pressure. Crude product was dissolved in benzene (50 ml), filtered. The filtrate was washed with 5% aqueous $NaHCO_3$ (2 x 15 ml), water (15 ml), and dried (Na_2SO_4). The solvent was removed under reduced pressure, the residue was distilled to obtain **16** as white crystals (b.p. 110°C/0.2 mm, m.p. 43°C, 3.0 g, 74%). ^{31}P-NMR ($CDCl_3$, δ): 30.0; ^{1}H-NMR ($CDCl_3$, δ): 7.12 (s, 1H), 6.93 (s, 1H), 3.98 (s, 3H), 3.09 (dq, 4H), 1.88 (d, $^2J_{P-H}$= 15 Hz, 3H), 1.03 (t, 6H). Anal. Calcd for $C_9H_{18}N_3OP$: C, 50.22; H, 8.43; N, 19.52. Found: C, 49.95; H, 8.44; N, 19.48.

(1-Methyl-*1H*-imidazol-2-yl)phosphonic acid *bis*-dimethylamide (17). The phosphorylation reaction was performed as described above with 1-methylimidazole (3.135 g , 26 mmol) and $POCl_3$. After standing 1 h at room temperature the stirred reaction mixture was treated with dimethylamine (80 mmol) at -20°C. Pyridine and unreacted amines were removed under reduced pressure. The remained oil was dissolved in benzene (50 ml), filtered. The filtrate was washed with 5% aqueous $NaHCO_3$ (2 x 15 ml), water (15 ml), and dried (Na_2SO_4). The volative products were removed under reduced pressure, the residue was distilled to yield **17** (2.0 g, 35%). Colourless oil, b.p. 120°C/0.2 mm.; ^{1}H-NMR ($CDCl_3$, δ): 7.17 (s, 1H), 7.00 (s, 1H), 3.99 (s, 3H), 2.75 (s, 6H), 2.65 (s, 6H). The compound **17** was N-alkylated by three-fold excess of methyl iodide by refluxing in benzene solution for 10 h. An analytical sample of the formed **1,3-dimethyl-2-hexamethylphosphamidatoimidazolium iodide** was prepared by recrystallization from methanol. White crystals, ^{31}P-NMR (CD_3OD:D_2O, δ): 13.0; ^{1}H-NMR (CD_3OD: D_2O, δ): 7.04 (s, 2H), 3.34 (s, 6H), 2.06 (s, 6H), 1.95 (s, 6H). Anal. Calc. for $C_9H_{20}IN_4OP$: C, 30.18, H, 5.63; N, 15.64. Found: C, 30.22; H, 5.60; N, 15.68.

(1-Ethyl-*1H*-imidazol-2-yl)phenylphosphinic acid morpholide (18). After the phosphorylation of 1-ethylimidazole (1g, 10.4 mmol) by $PhPOCl_2$ (1.63 ml, 11.5 mmol) in pyridine (6 ml) in the presence of triethylamine (1.71 ml, 12.5 mmol) for about 10 h the reaction mixture was treated carefully with morpholine (4 g, 46 mmol) and left overnight. Volative products was then evaporated *in vacuo* and the product was extracted with CCl_4. The solvent was removed, and the remained oil was chromatographed on silica gel Merck 60 with chloroform-methanol (7:1) as an eluent to give **18**. Recrystallized from hexane, white crystals, m.p. 105-106°C (2.53 g, 79.8%). ^{31}P-NMR ($CDCl_3$, δ): 18, ^{1}H-NMR ($CDCl_3$, δ): 7.70-7.95 (m, 2H), 7.35-7.70 (m, 3H), 7.25 (dd, $^3J_{H-H}$=$^4J_{P-H}$=1.2 Hz, 1H); 7.09 (dd,$^3J_{H-H}$=$^4J_{P-H}$=1.2 Hz, 1H); 4.44 (q, 2H), 3.69 (t, 4H), 2.90-3.40 (m, 4H), 1.33 (t, 3H). Anal. Calcd for $C_{15}H_{20}N_3O_2P$: C, 59.01; H, 6.60; N, 13.76. Found: C, 59.05; H, 6.62; N, 13.76.

Di-(1-methyl-*1H*-imidazol-2-yl)methylphosphine oxide (19). CH_3POCl_2 (2.0 g, 15 mmol) was dissolved in pyridine (50 ml) under dry nitrogen then 1-methylimidazole (3.542 g, 35 mmol) and triethylamine (5.54 ml, 40 mmol) were added. After standing 2 days at room temperature the volatile products were removed under reduced pressure. Crude product was dissolved in benzene (50 ml), filtered. The filtrate was washed with 5% aqueous $NaHCO_3$ (2 x 15 ml), water (15 ml), and dried (Na_2SO_4). The benzene solution was evaporated

to about 5 ml. The formed **19** (2.6 g, 78%) was recrystallized twice from benzene to obtain an analytical sample, m.p. 107-108°C. ^{31}P-NMR ($CDCl_3$, δ): 17 (q) ; ^{1}H-NMR ($CDCl_3$, δ): 7.20 (s, 2H), 7.05 (s, 2H), 3.96 (s, 6H), 2.29 (d, $^{2}J_{P-H}$= 15 Hz, 3H). Anal. Calcd for $C_9H_{13}N_4OP$: C, 48.21; H, 5.84; N, 24.99. Found: C, 47.98; H, 5.77; N, 24.56.

(1-Ethyl-5-nitro-*1H*-benzimidazol-2-yl)phenylphosphinic acid potassium salt (22). A solution of $PhPOCl_2$ (1.55 ml, 10,9 mmol) in pyridine (2 ml) was added to a stirred mixture of 1-ethyl-5-nitrobenzimidazole (2.091 g, 10,9 mmol), NEt_3 (2.08 ml, 15 mmol), and pyridine (15 ml) under dry nitrogen atmosphere. The formed dark brown solution was then heated at 40°C for about 8 days, taking precautions for the moisture not to get into the reaction flask. The reaction was monitored by ^{31}P-NMR - the signal of the reaction end product appears at 28 ppm (singlet; $PhPOCl_2$ gives a singlet at 33 ppm). After the reaction was complete the mixture was carefully poured into an aqueous solution of K_2CO_3 (20%, 50 ml). The precipitate was filtered off. The filtrate was evaporated, the remained solid was dried *in vacuo* over P_4O_{10} at 60°C for 2 h. The product was then extracted with dry methanol, the solvent was evaporated. Re-precipitated from methanol with benzene (2.8 g , 74%); contains traces of K_2CO_3, which do not intervene further transformations. ^{31}P-NMR (CD_3OD, δ): 11; ^{1}H-NMR (CD_3OD, δ): 8.63 (d, ^{4}J=2 Hz, 1H), 8.24 (dd, ^{3}J=8.5 Hz, ^{4}J=2 Hz, 1H) 7.80-8.05 (m, 2H), 7.69 (d, ^{3}J=8.5 Hz, 1H), 7.30-7.60 (m, 3H), 4.74 (q, 2H), 1.28 (t, 3H). Anal. Calcd for $C_{15}H_{13}KN_3O_4P$: C, 48.78; H, 3.55. Found: C, 48.76; H, 3.53.

(5-Amino-1-ethyl-*1H*-benzimidazol-2-yl)phenylphosphinic acid potassium salt (21). The solution of **22** (500 mg) in methanol (5 ml) with 50 mg of Pd / C (4% of Pd) was flushed with hydrogen for 5 min, and stirred under a hydrogen atmosphere for 2h. After the ^{1}H-NMR signals of **22** had disappeared, the mixture was filtered, and the Pd/C catalyst was washed with warm MeOH (2 × 1 ml). The filtrate was evaporated under reduced pressure. The product was re-precipitated from methanol with benzene, dried *in vacuo*, and used immediately for the next transformation. ^{31}P-NMR (CD_3OD, δ): 9; ^{1}H-NMR (CD_3OD, δ): 7.7-8.1 (m, 2H), 7.3-7.5 (m, 3H), 7.24 (d, ^{3}J=8.4 Hz, 1H), 7.05 (s, 1H), 6.81 (d, 1H), 4.58 (q, 2H), 1.18 (t 3H). IR (KBr, cm^{-1}): 3500 (N-H), 1250 (P=O).

(4-Trichloromethylphenyl)phosphonic dichloride (23). A solution of *p*-tolylphosphonous dichloride (1.75 g, 91 mmol) in CCl_4 (40 ml) was placed in a three-necked quartz reactor equipped with a gas inlet and a reflux condenser. Cl_2 was passed through the solution (30 ml/min) first without heating (about 15 min), then refluxing the mixture under UV-irradiation (600 W high-pressure mercury lamp). ^{1}H-NMR spectroscopy was used to follow the reaction. The methyl resonance (2.42 ppm, CCl_4-$CDCl_3$) disappeared gradually and appearance of CH_2Cl (4.49 ppm) and $CHCl_2$ (6.74 ppm) ^{1}H-NMR peaks was observed. The compound **24** formed white crystals. After all the aliphatic proton NMR signals had disappeared (7 - 8 h), the UV lamp was turned off, the heating bath removed and dry SO_2 was passed in lieu of Cl_2 until all crystals were dissolved and the green-yellow solution became almost colourless (~1 h). The solvent and $SOCl_2$ were removed under reduced pressure and the remained oil was distilled *in vacuo* to give 1-chloro-4-trichloromethylbenzene (b.p. 79-80°C/0.1 mm) and **23** (b.p. 140°C/0.1 mm, 28.4 g, 87%) as a viscous colorless oil which was crystallized on standing. An analytical sample of **23** was obtained by recrystallization from dry hexane, m.p. 56°C. ^{31}P-NMR ($CDCl_3$, δ): 32; ^{1}H-NMR ($CDCl_3$, δ): 7.6-8.7 (m); CCl_3 group reveals at 71,8 ppm in ^{13}C-NMR spectrum (CD_2Cl_2). Anal. Calcd for $C_7H_4Cl_5OP$: C, 26.91; H, 1.29. Found: C, 26.88; H, 1.22.

4-[(1-Ethyl-*1H*-benzimidazol-2-yl)-hydroxyphosphinoyl]benzoic acid (25). To a stirred mixture of 1-ethylbenzimidazole (3.98 g, 27.3 mmol), triethylamine (3.9 ml, 28.1 mmol), and pyridine (5 ml) a solution of **23** (8.52 g, 27.3 mmol) in pyridine (2 ml) was added under dry nitrogen. The mixture turned dark brown; it was left overnight. The product of the phosphorylation -- (1-ethyl-*1H*-benzimidazol-2-yl)-(4-trichloromethyl)phenylphosphinic chloride -- appears at 28 ppm in ^{31}P-NMR spectra. The mixture was poured into 10% aqueous

solution of KOH (300 ml). After refluxing for 2.5 h the solution was evaporated under reduced pressure by half. The precipitate formed was found to be 1,1'-diethyl-*1H,1'H*-[2,2']-*bis*-benzimidazolyl. It was filtered off and the filtrate was acidified to pH~3. Crude **25** was filtered, the filtrate was evaporated to dryness *in vacuo*, and another portion of **25** was extracted from the remained solid with methanol. The two portion of the product was combined, dissolved in minimal amount of 20% HCl. The black tar was removed by centrifugation, 20% KOH was added to pH~9, then 20% HCl to pH~3 under cooling in ice bath and stirring. The compound **25** formed was filtered, washed with cold 1% aqueous HCl, dried (4.8 g, 53.2%). An analytical sample was prepared by reaction of the acid **25** with K_2CO_3 in methanol, re-precipitation of the formed di-potassium salt from methanol with acetone, and converting the salt back into **25** in aqueous HCl solution (pH = 3). White powder, ^{31}P-NMR (CD_3OD, δ): 0.0; ^{1}H-NMR (CD_3OD, δ): 7.36-8.7 (m, 8H), 4.75 (q, 2H), 1.22 (t, 3H). A broad signal appeared at 4.2 ppm in ^{1}H-NMR spectrum of **25** in $(CD_3)_2SO$ which disappeared after addition of D_2O. IR (KBr, cm^{-1}): 3400 (OH), 1680 (C=O), 1210 (P=O). Anal. Calcd. for $C_{16}H_{15}N_2O_4P$: C, 58.18; H, 4.58; N, 8.48. Found: C, 57.89; H, 4.55; N, 8.35. Spectral data for the di-potassium salt: ^{31}P-NMR (D_2O, δ): 13.6; ^{1}H-NMR (CD_3OD, δ): 7.60-8.20 (m, 5H); 7.10-7.55 (m, 3H); 4.62 (q, 2H); 1.16 (t, 3H).

{5-[4-(2,5-dioxopyrrolidin-1-yloxicarbonyl)-butyrylamino]-1-ethyl-*1H*-benzimidazol-2-yl}phenyl-phosphinic acid potassium salt (26). A solution of **27** (169.5 mg, 0.684 mmol) in dry DMF (1 ml) was added to a stirred suspension of **21** (218.6 mg, 0.644 mmol) and K_2CO_3 in 5 ml of dry DMF. After stirring for 12 h the mixture was filtered, the solvent was evaporated. The remained solid was washed with dry benzene, by-products and starting materials were removed by extraction with dry chloroform. The product (210 mg) was dried *in vacuo* over P_4O_{10}. ^{31}P-NMR (CD_3OD, δ): 8.5; ^{1}H-NMR (CD_3OD, δ): 7.84-7.97 (m, 3H), 7.46 (m, 5H), 4.67 (q, 2H), 2.65 (s, 4H), 2.42 (t, 2H), 2.29 (t, 2H), 1.24 (t, 3H). ^{1}H-NMR spectrum of **26** in $(CD_3)_2SO$ reveals two singlets at 10.1 and 10 ppm, which can be assigned to NH proton (two geometric isomers of the amide). Anal. Calcd. for $C_{24}H_{24}N_4O_7PK$: C, 52.36; H, 4.39; N, 10.18. Found: C, 52.95; H, 4.25; N, 9.98.

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