Synthesis of pyridine-containing α-hydrazino phosphonates by two-component catalytic procedure

E. D. Matveeva, T. A. Podrugina, I. N. Kolesnikova, and N. S. Zefirov*

Department of Chemistry, M. V. Lomonosov Moscow State University, 1 Leninskie Gory, 119992 Moscow, Russian Federation. Fax: +7 (495) 939 0290. E-mail: matveeva@org.chem.msu.ru

Pyridine-containing α-hydrazino phosphonates were synthesized in high yields by reaction of hydrazones of pyridine series with diethyl phosphite in the presence of [tetra(*tert*-butyl)-phthalocyanine]aluminum chloride as a catalyst.

Key words: hydrazones, phosphorylation, pyridine derivatives, the Pudovik reaction, [tetra(*tert*-butyl)phthalocyanine]aluminum chloride, diethyl phosphite.

One of the approaches to the potent twin-drugs is the combination of two pharmacophores in one molecule. The aim of the present work is the combination of such pharmacophores as phosphonate group and the pyridine ring, which is the principal fragment of a series of vitamins and medications,[1—3] in one molecule. Earlier, we developed procedure toward hybrid molecules of this type, which involved catalytic preparation of α-amino phosphonates in the presence of [tetra(*tert*-butyl)phthalocyanine]aluminum chloride (^{t}PcAlCl). This method was applied for the synthesis of α-amino phosphonates on the base of 2-, 3-, and 4-aminopyridines.[4] Catalysis with ^{t}PcAlCl was also successfully used for hydrophosphorylation of azines and hydrazones.[5—7] Present work is devoted to the extension of this catalytic procedure on the synthesis of hydrazino phosphonates from pyridine-containing hydrazones.

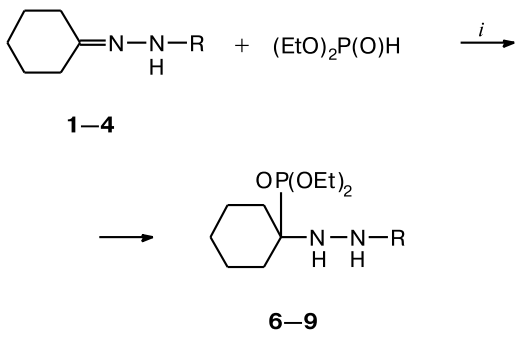
Hydrazones **1—5** bearing the pyridine ring were prepared by the reaction of cyclohexanone with 2-hydrazinopyridine, pyridinecarboxhydrazides, and 6-hydrazinopyridine-3-carboxhydrazide in 85—90% yield.

Hydrophosphorylation of pyridine-containing hydrazones **1—4** in the presence of ^{t}PcAlCl resulted in hitherto unknown α-hydrazino phosphonates **6—9** (Scheme 1, Table 1).

As it can be seen from the data in Table 1, the reaction of cyclohexanone pyridin-2-ylhydrazone (**1**) with diethyl phosphite proceeded with low rate even under catalytic conditions and afforded α-hydrazino phosphonate **6** in 35% yield.

Due to electron-withdrawing carbonyl group, which increased the electrophilicity of the imine bond, hydrophosphorylation of acylhydrazones derived from hydrazides of picolinic (**2**), nicotinic (**3**), and isonicotinic acids (**4**) proceeded noticeably faster and the correspond-

Scheme 1



i. ^{t}PcAlCl, argon, 80 °C.

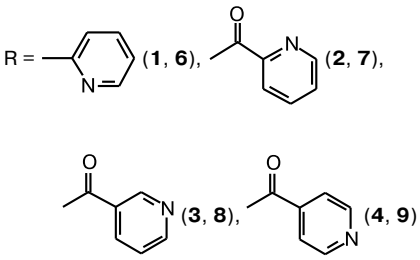


Table 1. Synthetic conditions and yields of pyridine-containing α-hydrazinophosphonates **6—9**

Starting hydrazone	τ/h	Product	Yield (%)
1	50	**6**	35
2	2	**7**	85
3	8	**8**	80
4	8	**9**	75

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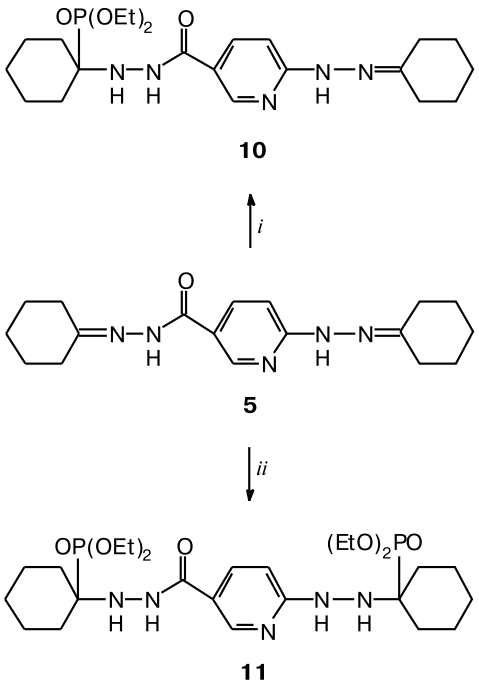
ing α-hydrazino phosphonates **7—9** were prepared in 75—85% yield within 2—8 h.

The difference in the reactivity of two imine bonds in dihydrazone **5** makes it possible to develop conditions for chemoselective mono- (compound **10**) and diphosphorylations (compound **11**). Thus, when the reaction was carried out for 6 h, monophosphonate **10** was isolated in 75% yield, while prolongation of the reaction time up to 40 h gave diphosphonate **11** as the main product in 50% yield (Scheme 2).

Scheme 2



i. $(EtO)_2P(O)H$, ^tPcAlCl, 80 °C, 6 h;
ii. $(EtO)_2P(O)H$, ^tPcAlCl, 80 °C, 40 h.

Structures of α-hydrazino phosphonates **6—11** were established by IR spectroscopy, ^1H, ^{13}C, and ^{31}P NMR spectroscopy, and confirmed by elemental analysis. The IR spectra of the compounds synthesized exhibited the absorption bands at 1230—1260 and 3230—3290 cm^{-1} attributed to the P=O group and the NH group, respectively. In the ^{31}P NMR spectra of α-hydrazino phosphonates **6—10**, the signals for the phosphorus atoms were observed at the range of δ 27.85—30.51. The ^{31}P NMR spectra of α-hydrazino phosphonate **11** contained two signals for the phosphorus atoms at δ 28.27 and 29.93. In the ^{13}C NMR spectra of compounds **6—11** the signals for the C(α) atoms appeared at the range of δ 58.38—58.93. ($^1J_{C,P}$ = 142.0—162.5 Hz). Other signals in ^{13}C and ^{31}P NMR spectra confirm also the structures of the compounds synthesized.

In summary, the developed catalytic procedure allows the synthesis of hitherto unknown pyridine-containing α-hydrazino phosphonates.

Experimental

NMR spectra were run on a Bruker Avance 400 instrument (400.13 (^1H), 100.61 (^{13}C), and 161.98 MHz (^{31}P)) in $CDCl_3$ relative of Me_4Si (^1H, ^{13}C, internal standard) and 85% aqueous H_3PO_4 (^{31}P, external standard). IR spectra were recorded on a UR-20 in CCl_4. Elemental analysis was carried out on a Vario-II CHN-analyzer.

Diethyl phosphite (Aldrich) was used as purchased. [Tetra-(*tert*-butyl)phthalocyanine]aluminum chloride was synthesized according to the known procedure.[8] The course of the reactions and the purity of compounds were monitored by TLC carried out on a ALUGRAM SIL G/UV_{254} plates. Column chromatography was performed on silica gel (MN Kieselgel 60, 0.04—0.063 mm).

Cyclohexanone pyridin-2-ylhydrazone (1). A mixture of cyclohexanone (150 mg, 1.5 mmol) and 2-hydrazinopyridine (110 mg, 1 mmol) was stirred at ambient temperature for 0.5 h, the precipitate that formed was filtered off, washed with diethyl ether, and dried *in vacuo*. Yield 160 mg (85%), m.p. 92—93 °C (*cf.* Ref. 9: 92—92.5 °C).

Synthesis of hydrazones 2—5 (general procedure). A mixture of cyclohexanone (9 mmol) and the corresponding hydrazide (3 mmol) was refluxed for 3 h, the reaction mixture was cooled to ambient temperature, the precipitate that formed was filtered off, washed with diethyl ether, and dried *in vacuo*.

***N´*-Cyclohexylidenepyridine-2-carboxhydrazide (2).** Yield 90%, m.p. 148—149 °C (*cf.* Ref. 10: 148—150 °C).

***N´*-Cyclohexylidenepyridine-3-carboxhydrazide (3).** Yield 92%, m.p. 115—116 °C (*cf.* Ref. 11: 116—118 °C).

***N´*-Cyclohexylidenepyridine-4-carboxhydrazide (4).** Yield 90%, m.p. 166—168 °C (*cf.* Ref. 12: 168—169.5 °C).

***N´*-Cyclohexylidene-6-(2-cyclohexylidenehydrazino)pyridine-3-carboxhydrazide (5).** Yield 88%, m.p. 294—296 °C. ^1H NMR, δ: 1.53—1.61 (m, 12 H, cycl.); 2.19—2.28 (m, 8 H, CH_2, cycl.); 4.18 (br.s, 2 H, NHPy, NHC(O)); 7.08 (d, 1 H, Py, $^3J_{H,H}$ = 8.9 Hz); 7.91 (d, 1 H, Py, $^3J_{H,H}$ = 5.8 Hz); 8.40 (s, 1 H, Py). ^{13}C NMR, δ: 25.35, 25.49, 25.72, 25.92, 26.03, 26.89, 26.95, 27.77, 35.23 (CH_2, cycl.); 106.49, 119.78, 137.64, 147.10, 155.56 (C, Py); 158.71, 163.46 (C=N); 166.46 (C=O). IR, ν/cm^{-1}: 1600 (C=N), 1640 (C=O); 3240 (NH). Found (%): C, 66.34; H, 7.50; N, 21.30. $C_{18}H_{25}N_5O$. Calculated (%): C, 66.03; H, 7.70; N, 21.39.

Synthesis of α-hydrazinophosphonates 6—11 (general procedure). Diethyl phosphite (5—8 mmol) and ^tPcAlCl (0.05 mmol) were added to the corresponding hydrazone (1 mmol). The reaction mixture was stirred under argon at 80 °C until complete (TLC monitoring). The volatiles were removed *in vacuo*, the residue was dissolved in CH_2Cl_2—MeOH (70 : 1) and the product was isolated by column chromatography (silica gel, column height 15 cm, diameter 1.5—2.0 cm).

Diethyl 1-[2-(pyridin-2-yl)hydrazino]cyclohexylphosphonate (6) was synthesized from hydrazone **1** at reactant ratio of 1 : 5, the reaction time was 50 h. Yield 35%. ^1H NMR, δ: 1.34 (t, 6 H, 2 Me, $^3J_{H,H}$ = 7.0 Hz); 1.41—1.50 (m, 2 H, CH_2, cycl.); 1.59—1.75 (m, 6 H, CH_2, cycl.); 1.82—1.89 (m, 2 H, CH_2, cycl.); 3.89 (br.s, 1 H, NH); 4.12—4.20 (m, 4 H, 2 OCH_2); 6.57—6.60 (m, 2 H, Py); 7.06 (d, 1 H, Py, $^3J_{H,H}$ = 8.6 Hz);

7.45—7.49 (m, 1 H, Py); 8.02 (br.m, 1 H, NH). ^{13}C NMR, δ: 16.67 (d, Me, $^{3}J_{C,P}$ = 5.1 Hz); 20.31 (d, $^{3}J_{H,P}$ = 11.0 Hz); 25.35, 27.61 (CH_2, cycl.); 58.38 (d, C(α), $^{1}J_{C,P}$ = 142.0 Hz); 62.36 (d, OCH_2, $^{2}J_{C,P}$ = 8.0 Hz); 106.92, 113.99, 137.61, 147.61, 161.06 (C, Py). ^{31}P NMR, δ: 30.51. IR, ν/cm^{-1}: 1040, 1080 (P—O—C); 1230 (P=O); 3290, 3330 (NH). Found (%): C, 55.13; H, 8.15; N, 12.64. $C_{15}H_{26}N_3O_3P$. Calculated (%): C, 55.03; H, 8.01; N, 12.84.

Diethyl 1-[2-(pyridin-2-ylcarbonyl)hydrazino]cyclohexylphosphonate (7) was synthesized from hydrazone **2** at reactant ratio of 1 : 5, the reaction time was 2 h. Yield 85%. ^{1}H NMR, δ: 1.15—1.27 (m, 1 H, CH_2, cycl.); 1.35 (t, 6 H, 2 Me, $^{3}J_{H,H}$ = 7.1 Hz); 1.49—1.57 (m, 2 H, CH_2, cycl.); 1.61—1.76 (m, 5 H, CH_2, cycl.); 1.86—1.97 (m, 2 H, CH_2, cycl.); 4.17—4.25 (m, 4 H, 2 OCH_2); 4.83 (br.s, 1 H, N<u>H</u>NHC(O)); 7.37 (ddd, 1 H, Py, $^{3}J_{H,H}$ = 4.8 Hz, $^{3}J_{H,H}$ = 4.6 Hz, $^{3}J_{H,H}$ = 1.2 Hz); 7.79 (ddd, 1 H, Py, $^{3}J_{H,H}$ = 7.5 Hz, $^{3}J_{H,H}$ = 7.6 Hz, $^{3}J_{H,H}$ = 1.7 Hz); 8.09 (d, 1 H, Py, $^{3}J_{H,H}$ = 7.9 Hz); 8.54 (d, 1 H, Py, $^{3}J_{H,H}$ = 6.4 Hz); 10.01 (br.s, 1 H, NHN<u>H</u>C(O)). ^{13}C NMR, δ: 16.51 (d, Me, $^{3}J_{C,P}$ = = 5.1 Hz); 19.89 (d, $^{3}J_{H,P}$ = 10.9 Hz); 25.11, 27.48 (CH_2, cycl.); 58.72 (d, C(α), $^{1}J_{C,P}$ = 162.5 Hz); 62.80 (d, OCH_2, $^{2}J_{C,P}$ = = 7.3 Hz); 121.95, 125.98, 137.14, 148.41, 149.20 (C, Py); 161.06 (s, C=O). ^{31}P NMR, δ: 28.16. IR, ν/cm^{-1}: 1040, 1080 (P—O—C); 1230 (P=O); 1690 (C=O); 3260 (NH). Found (%): C, 54.15; H, 7.25; N, 11.71. $C_{16}H_{26}N_3O_4P$. Calculated (%): C, 54.08; H, 7.37; N, 11.82.

Diethyl 1-[2-(pyridin-3-ylcarbonyl)hydrazino]cyclohexylphosphonate (8) was synthesized from hydrazone **3** at reactant ratio of 1 : 5, the reaction time was 8 h. Yield 80%. ^{1}H NMR, δ: 1.17—1.25 (m, 1 H, CH_2, cycl.); 1.35 (t, 6 H, 2 Me, $^{3}J_{H,H}$ = 7.1 Hz); 1.50—1.73 (m, 7 H, CH_2, cycl.); 1.90—1.95 (m, 2 H, CH_2, cycl.); 4.16—4.23 (m, 4 H, 2 OCH_2); 5.41 (br.d, 1 H, N<u>H</u>NHC(O), $^{3}J_{H,P}$ = 28.8 Hz); 7.35 (dd, 1 H, Py, $^{3}J_{H,H}$ = 7.8 Hz, $^{3}J_{H,H}$ = = 4.8 Hz); 8.06 (d, 1 H, Py, $^{3}J_{H,H}$ = 7.9 Hz); 8.70 (d, 1 H, Py, $^{3}J_{H,H}$ = 4.8 Hz); 9.03 (s, 1 H, Py); 9.13 (br.s, 1 H, NHN<u>H</u>C(O)). ^{13}C NMR, δ: 16.53 (d, Me, $^{3}J_{C,P}$ = 4.8 Hz); 19.89 (d, $^{3}J_{H,P}$ = = 10.5 Hz); 25.12, 27.62 (CH_2, cycl.); 58.93 (d, C(α), $^{1}J_{C,P}$ = 162.2 Hz); 63.05 (d, OCH_2, $^{2}J_{C,P}$ = 7.2 Hz); 123.37, 128.49, 134.38, 148.21, 152.25 (C, Py); 162.30 (s, C=O). ^{31}P NMR, δ: 28.13. IR, ν/cm^{-1}: 1040, 1080 (P—O—C); 1230 (P=O); 1660 (C=O); 3290 (NH). Found (%): C, 54.27; H, 7.39; N, 11.75. $C_{16}H_{26}N_3O_4P$. Calculated (%): C, 54.08; H, 7.37; N, 11.82.

Diethyl 1-[2-(pyridin-4-ylcarbonyl)hydrazino]cyclohexylphosphonate (9) was synthesized from hydrazone **4** at reactant ratio of 1 : 5, the reaction time was 8 h. Yield 75%. ^{1}H NMR, δ: 1.12—1.20 (m, 1 H, CH_2, cycl.); 1.30 (t, 6 H, 2 Me, $^{3}J_{H,H}$ = 7.1 Hz); 1.45—1.65 (m, 7 H, CH_2, cycl.); 1.82—1.90 (m, 2 H, CH_2, cycl.); 4.11—4.18 (m, 4 H, 2 OCH_2); 5.39 (br.s, 1 H, N<u>H</u>NHC(O)); 7.60 (d, 2 H, Py, $^{3}J_{H,H}$ = 4.3 Hz); 8.65 (d, 2 H, Py, $^{3}J_{H,H}$ = 4.3 Hz); 9.33 (br.s, 1 H, NHN<u>H</u>C(O)). ^{13}C NMR, δ: 16.48 (d, Me, $^{3}J_{C,P}$ = 5.1 Hz); 19.76 (d, $^{3}J_{H,P}$ = 11.0 Hz); 25.01, 27.49 (CH_2, cycl.); 58.80 (d, C(α), $^{1}J_{C,P}$ = 162.4 Hz); 63.07 (d, OCH_2, $^{2}J_{C,P}$ = 7.4 Hz); 120.60, 139.68, 150.46 (C, Py); 161.73 (s, C=O). ^{31}P NMR, δ: 27.85. IR, ν/cm^{-1}: 1040, 1080 (P—O—C); 1240 (P=O); 1670 (C=O); 3290 (NH). Found (%): C, 54.21; H, 7.43; N, 11.75. $C_{16}H_{26}N_3O_4P$. Calculated (%): C, 54.08; H, 7.37; N, 11.82.

Diethyl 1-(2-{[6-(2-cyclohexylidenehydrazino)pyridin-3-yl]carbonyl}hydrazino)cyclohexylphosphonate (10) was synthesized from hydrazone **5** at reactant ratio of 1 : 5, the reaction time was 6 h. Yield 75%. ^{1}H NMR, δ: 1.16—1.23 (m, 1 H, CH_2, cycl.); 1.33 (t, 6 H, 2 Me, $^{3}J_{H,H}$ = 7.1 Hz); 1.47—1.75 (m, 13 H, CH_2, cycl.); 1.86—1.95 (m, 2 H, CH_2, cycl.); 2.30—2.36 (m, 4 H, CH_2, cycl.); 4.12—4.21 (m, 4 H, 2 OCH_2); 5.43 (dd, 1 H, N<u>H</u>NHC(O), $^{3}J_{H,P}$ = 29.1 Hz, $^{3}J_{H,H}$ = 6.8 Hz); 7.17 (d, 1 H, Py, $^{3}J_{H,H}$ = 9.3 Hz); 7.88 (d, 1 H, Py, $^{3}J_{H,H}$ = 8.8 Hz); 8.27 (br.s, 1 H, NHPy); 8.54 (s, 1 H, Py); 8.73 (d, 1 H, NHN<u>H</u>C(O), $^{3}J_{H,H}$ = 6.3 Hz). ^{13}C NMR, δ: 16.55 (d, Me, $^{3}J_{C,P}$ = 5.1 Hz); 19.86, 19.97, 25.13, 25.66, 25.73, 25.86, 27.01, 27.52, 35.41 (CH_2, cycl.); 58.91 (d, C(α), $^{1}J_{C,P}$ = 162.5); 62.90 (d, OCH_2, $^{2}J_{C,P}$ = 7.4 Hz); 106.09, 119.38, 136.24, 147.57, 153.70 (C, Py); 159.14 (s, C=N); 163.01 (s, C=O). ^{31}P NMR, δ: 28.33. IR, ν/cm^{-1}: 1025, 1060 (P—O—C); 1225 (P=O); 1650 (C=O); 3260 (NH). Found (%): C, 56.84; H, 7.89; N, 14.98. $C_{22}H_{36}N_5O_4P$. Calculated (%): C, 56.76; H, 7.79; N, 15.04.

Diethyl 1-{2-[5-({2-[1-(diethyloxyphosphoryl)cyclohexyl]hydrazino}carbonyl)pyridin-2-yl]hydrazino}cyclohexylphosphonate (11) was synthesized from hydrazone **5** at reactant ratio of 1 : 8, the reaction time was 40 h. Yield 50%. ^{1}H NMR, δ: 1.17—1.25 (m, 1 H, CH_2, cycl.); 1.33, 1.36 (both t, 12 H, 2 Me, $^{3}J_{H,H}$ = 7.1 Hz); 1.45—1.58 (m, 4 H, CH_2, cycl.); 1.60—1.72 (m, 13 H, CH_2, cycl.); 1.73—1.93 (m, 2 H, CH_2, cycl.); 3.98 (br.s, 1 H, N<u>H</u>NHPy); 4.13—4.22 (m, 8 H, 4 OCH_2); 5.34 (d, 1 H, N<u>H</u>NHC(O), $^{3}J_{H,P}$ = 27.1 Hz); 7.04 (d, 1 H, Py, $^{3}J_{H,H}$ = 8.8 Hz); 7.07 (br.s, 1 H, NHN<u>H</u>Py); 7.85 (dd, 1 H, Py, $^{3}J_{H,H}$ = 8.9 Hz, $^{4}J_{H,H}$ = 2.0 Hz); 8.51 (s, 1 H, Py); 8.71 (br.s, 1 H, NHN<u>H</u>C(O)). ^{13}C NMR, δ: 16.55 (d, Me, $^{3}J_{C,P}$ = 5.8 Hz); 16.63 (d, Me, $^{3}J_{C,P}$ = 5.1 Hz); 19.89 (d, $^{3}J_{C,P}$ = 10.9 Hz); 20.29 (d, $^{3}J_{C,P}$ = 11.0 Hz); 25.18 (d, $^{3}J_{C,P}$ = 11.0 Hz); 27.49 (CH_2, cycl.); 58.38 (d, C(α), $^{1}J_{C,P}$ = 142.7 Hz); 58.91 (d, C(α), $^{1}J_{C,P}$ = = 161.7 Hz); 62.54, 62.94 (both d, OCH_2, $^{2}J_{C,P}$ = 7.3 Hz); 105.74, 118.37, 136.03, 147.66, 162.23 (C, Py); 163.22 (s, C=O). ^{31}P NMR, δ: 28.27, 29.93. IR, ν/cm^{-1}: 1040, 1060 (P—O—C); 1225 (P=O); 1645 (C=O); 3280 (NH). Found (%): C, 51.43; H, 7.72; N, 11.39. $C_{26}H_{47}N_5O_7P_2$. Calculated (%): C, 51.73; H, 7.85; N, 11.60.

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