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Mendeleev Commun., 2009, **19**, 303–305

Mendeleev Communications

Friedländer reaction in the synthesis of 2-(phosphoryl)alkyl-substituted 1,6-naphthyridines

Pavel S. Lemport,* Georgy V. Bodrin, Andrey I. Belyakov, Pavel V. Petrovskii, Anna V. Vologzhanina and Edward E. Nifant'ev

A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 119991 Moscow, Russian Federation. Fax: +7 495 135 6549; e-mail: pav-lemport@yandex.ru

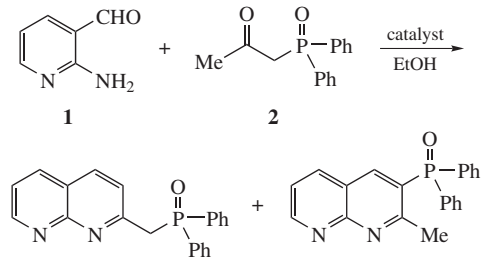
DOI: 10.1016/j.mencom.2009.11.002

First 2-(phosphoryl)alkyl-substituted 1,6-naphthyridines have been synthesized by the Friedländer reaction between 4-amino-3-formylpyridine and phosphorus-containing ketones; their structures have been confirmed by ^{1}H, ^{13}C and ^{31}P NMR spectroscopy and X-ray diffraction analysis.

Naphthyridines, aromatic systems with two endocyclic nitrogen atoms, are of interest[1] because they display various kinds of biological activity.[2] Nonetheless, phosphorus-containing naphthyridines are poorly studied.

The Friedländer annulation is an important method for preparing naphthyridines. The mechanism of this reaction is not well understood in spite of the fact that the reaction has been discovered more than 125 years ago. We have shown recently that the above reaction can be used in the molecular design of 1,8-naphthyridine ligand systems.[3,4] In a continuation of our study on the design of new interesting organophosphorus molecules, we have attempted to apply this method to the synthesis of previously unknown 2-(phosphoryl)alkyl-substituted 1,6-naphthyridines.

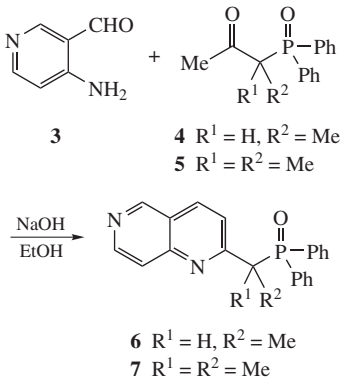
It is well known that the Friedländer annulation of aminonicotinic aldehydes with unsymmetrical functionalized 2-alkanones can result in a mixture of 2-monosubstituted and 2,3-disubstituted products in different ratios depending on the structures of the ketone and the catalyst.[5] We found[3] that 2-amino-3-formylpyridine **1** reacts with the simplest β-ketophosphine oxide, namely, diphenylphosphorylacetone **2** (DPA), to give two phosphorus-containing products irrespective of the type of catalyst used (Scheme 1).



Scheme 1

Taking into consideration those experiments, we carried out the reaction of 4-amino-3-formylpyridine **3** with DPA derivatives **4** and **5** containing a sole active in this reaction terminal α-methyl group. The reaction readily proceeds in the presence of catalytic amounts of NaOH to afford naphthyridines **6** and **7** in good yields (Scheme 2).

4-Amino-3-formylpyridine **3** proved to be slightly less reactive in comparison with 2-amino-3-formylpyridine **1**. The reaction of ketone **5** with aldehyde **1** proceeds at ambient temperature,[3]



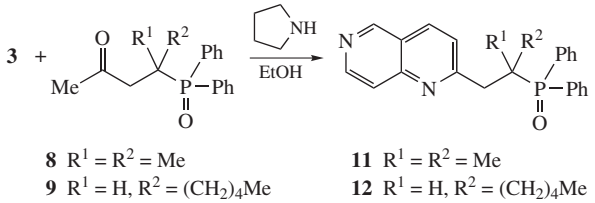
Scheme 2

whereas 4-aminonicotinic aldehyde requires heating when it reacts with compounds **4** and **5**.

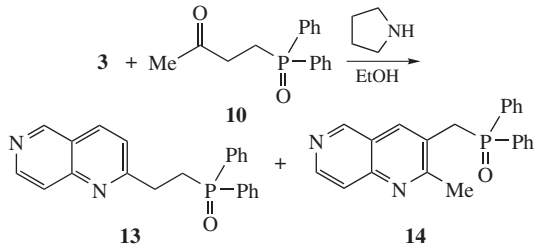
Along with the methylated derivatives of diphenylphosphorylacetone, other ketones **8**–**10** containing reactive α-methyl groups were also involved into condensation with aldehyde **3**. Note that these ketones also contain α-methylene groups capable of participating in the Friedländer reaction. Nevertheless, these groups are less reactive in comparison with those in DPA. We found[4] that ketones **8** and **10** readily react with 2-aminonicotinic aldehyde. The target 2-substituted 1,8-naphthyridines can be obtained in good yields using pyrrolidine as a catalyst that provides high regioselectivity of condensation process in some cases.[4,6]

We attempted to apply this method to the synthesis of corresponding 2-substituted 1,6-naphthyridines. The reaction proceeds with high regioselectivity only for ketones **8** and **9** to give phosphorus-containing naphthyridines **11** and **12** (Scheme 3).

In its turn, ketone **10** reacts with aldehyde **3** to yield a mixture of isomeric 2-monosubstituted and 2,3-disubstituted 1,6-naphthyridines **13** and **14** at an approximate ratio of 3:7 (Scheme 4).



Scheme 3



Scheme 4

Naphthyridines **6**, **7**, **11** and **12** are slightly coloured solids readily soluble in DMSO, $CHCl_3$, and EtOH but poorly soluble in hexane and diethyl ether. The synthesized phosphorus-containing compounds have been characterized by melting points, elemental analysis data, and ^1H, ^{13}C and ^{31}P NMR spectra.† The structure of compound **7** was confirmed by X-ray diffraction data, the ORTEP view of **7** is given in Figure 1.‡

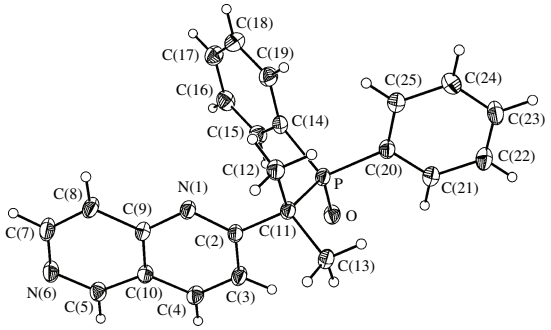


Figure 1 General view of **7** in representation of atoms by thermal ellipsoids at the 50% probability level. Selected bond lengths (Å): P–O 1.4908(19), P–C(14) 1.815(3), P–C(20) 1.823(3), P–C(11) 1.857(3), C(11)–C(12) 1.529(3), C(11)–C(13) 1.540(3), C(11)–C(2) 1.532(3), N(1)–C(2) 1.329(3), C(2)–C(3) 1.423(3), C(3)–C(4) 1.362(4), C(4)–C(10) 1.420(3), C(10)–C(5) 1.418(3), C(5)–N(6) 1.321(3), N(6)–C(7) 1.358(4), C(7)–C(8) 1.368(4), C(8)–C(9) 1.418(3), C(9)–C(10) 1.405(3), C(9)–N(1) 1.373(3).

X-ray diffraction study shows that all P–C distances in the molecule are consistent with single bond lengths, whereas the P–O distance corresponds to a double bond. The bond lengths in the heteroaromatic fragment of 1,6-naphthyridine (Napy) are

† The NMR spectra were recorded on a Bruker Avance-400 spectrometer operating at 400.1 (^1H), 100.6 (^{13}C) and 162.0 MHz (^{31}P) in $CDCl_3$ solutions using the proton signal of the $CHCl_3$ in $CDCl_3$ as an internal reference (^1H) and 85% H_3PO_4 (^{31}P) as external reference.

All reactions were conducted in an inert gas atmosphere.

4-Amino-3-formylpyridine **3** was obtained as described elsewhere.[7] Compound **5** was synthesized as reported previously.[3] Ketones **8** and **10** were obtained by the previously described procedure.[4]

2-(Diphenylphosphoryl)butan-3-one **4**. Sodium hydride (0.50 g of 60% suspension in mineral oil) was added in small portions to a magnetically stirred solution of 2.58 g (0.01 mol) of diphenylphosphorylacetone **2** in 20 ml of THF. After completion of the reaction detected with a bubbler, 0.8 ml of CH_3I was added and the reaction mixture was left to stand for 6 h at ambient temperature. The solvent was removed under reduced pressure, the residue was dissolved in $CHCl_3$, and the solution was washed twice with water, dried with K_2CO_3, and evaporated to afford a yellow solid. The residue was recrystallized from hexane to give 1.90 g (70%) of compound **4** as a white powder; mp 133–134 °C. ^{31}P NMR ($CDCl_3$) δ: 30.0. ^1H NMR ($CDCl_3$) δ: 7.80–7.73 (m, 4H, *m*-Ph), 7.55–7.25 (m, 6H, *o*-Ph, *p*-Ph), 3.65–3.60 (m, 1H, CH–P), 2.21 (s, 3H, MeCO), 1.39 (dd, 3H, *Me*CH, $J_{H,H}$ 7.2 Hz, $J_{H,P}$ 16.2 Hz).

Naphthyridines **6** *and* **7** *(general procedure).* A solution of aldehyde **3** (2.5 mmol) and corresponding ketone **4** or **5** (2.5 mmol) in EtOH (8 ml) was added with stirring to a suspension of 0.02 g of NaOH in 2 ml of EtOH at ambient temperature. The reaction mixture was refluxed for 30 min and concentrated in a vacuum. The residue was dissolved in $CHCl_3$, and the solution was washed twice with water and dried with K_2CO_3. The solvent was removed and the residue was triturated with diethyl ether to give the target product as a powder.

2-[1-(Diphenylphosphoryl)ethyl]-1,6-naphthyridine **6**. A white powder. Yield 70%, mp 159–160 °C. ^{31}P NMR ($CDCl_3$) δ: 32.9. ^1H-{^{31}P} NMR ($CDCl_3$) δ: 9.16 (s, 1H, Napy-H^5), 8.66 (d, 1H, Napy-H^7, *J* 5.9 Hz), 8.16 (d, 1H, Napy-H^4, *J* 8.6 Hz), 7.90 (d, 3H, 2*o*-Ph + Napy-H^3, *J* 8.2 Hz), 7.68 (d, 1H, Napy-H^8, *J* 5.9 Hz), 7.64 (d, 2H, *o*-Ph, *J* 7.1 Hz), 7.55–7.48 (m, 3H, 2*m*-Ph, *p*-Ph), 4.21 (q, 1H, CH–P, *J* 7.4 Hz), 1.68 (d, 3H, CH*Me*, *J* 7.4 Hz). ^{13}C NMR ($CDCl_3$) δ: 164.2 (d, 1C, Napy-C^2, *J* 3.7 Hz), 152.37 (s, 1C, Napy-C^5), 149.6 (s, 1C, Napy-C^9), 146.78 (s, 1C, Napy-C^7), 135.8 (s, 1C, Napy-C^4), 131.7 (d, 2C, *p*-Ph, *J* 7.9 Hz), 131.4 (d, 2C, *p*-Ph, *J* 7.9 Hz), 131.2 (d, 2C, P–C_{Ph}, *J* 100.1 Hz), 130.9 (d, 4C, *m*-Ph, *J* 15.7 Hz), 128.6 (d, 2C, *o*-Ph, *J* 31.4 Hz), 128.0 (d, 2C, *o*-Ph, *J* 29.4 Hz), 122.8 (s, 1C, Napy-C^8), 122.4 (s, 1C, Napy-C^{10}), 121.3 (s, 1C, Napy-C^3), 44.5 (d, 1C, P–*C*HMe, *J* 63.8 Hz), 14.22 (d, 2C, P–CH*Me*, *J* 3.0 Hz).

2-[(1-Diphenylphosphoryl-1-methyl)ethyl]-1,6-naphthyridine **7**. A pale yellow powder. Yield 74%, mp 136–137 °C. ^{31}P NMR ($CDCl_3$) δ: 37.4. ^1H-{^{31}P} NMR ($CDCl_3$) δ: 9.18 (s, 1H, Napy-H^5), 8.70 (d, 1H, Napy-H^7, *J* 5.9 Hz), 8.08 (d, 1H, Napy-H^4, *J* 8.8 Hz), 7.80 (d, 1H, Napy-H^3, *J* 8.8 Hz), 7.74 (d, 1H, Napy-H^8, *J* 5.8 Hz), 7.68 (d, 4H, *o*-Ph, *J* 7.4 Hz), 7.43 (t, 2H, *p*-Ph, *J* 7.4 Hz), 7.33 (t, 4H, *m*-Ph, *J* 7.4 Hz), 1.81 (s, 6H, 2Me). ^{13}C NMR ($CDCl_3$) δ: 166.9 (s, 1C, Napy-C^2), 152.2 (s, 1C, Napy-C^5), 149.0 (s, 1C, Napy-C^9), 146.7 (s, 1C, Napy-C^7), 134.8 (s, 1C, Napy-C^4), 132.2 (d, 4C, *m*-Ph, *J* 22.5 Hz), 131.4 (d, 2C, *p*-Ph, *J* 5.9 Hz), 130.6 (d, 2C, P–C_{Ph}, *J* 95.4 Hz), 127.8 (d, 4C, *o*-Ph, *J* 30.1 Hz), 122.9 (s, 1C, Napy-C^8), 121.9 (s, 1C, Napy-C^{10}), 121.7 (s, 1C, Napy-C^3), 46.4 (d, 1C, P–*C*HMe$_2$, *J* 62.5 Hz), 23.6 (s, 2C, P–C*Me*$_2$).

4-(Diphenylphosphoryl)nonan-2-one **9**. The compound was obtained similarly to compound **8** according to the previously described procedure starting from *trans*-non-3-en-2-one (2.37 g, 0.0168 mol). Yield 5.30 g (92%), mp 104–105 °C. ^{31}P NMR ($CDCl_3$) δ: 36.6. Found (%): C, 73.65; H, 8.04; P, 9.08. Calc. for $C_{21}H_{27}O_2P$ (%): C, 73.66; H, 7.95; P, 9.05.

Naphthyridines **11** *and* **12** *(general procedure)*. A solution of aldehyde **3** (5 mmol) and corresponding ketone **8** or **9** (5 mmol) in ethanol (10 ml) was added to a catalyst prepared from 0.45 ml of pyrrolidine and one drop of H_2SO_4. The mixture was allowed to stand for a day at ambient temperature. The solvent was distilled off, the residue was dissolved in $CHCl_3$, the solution was washed twice with water and dried with K_2CO_3. Chloroform was removed, the residue was triturated with diethyl ether and recrystallized from ethyl acetate–hexane mixture (1:1).

2-[(2-Diphenylphosphoryl-2-methyl)propyl]-1,6-naphthyridine **11**. A white powder. Yield 76%, mp 167–168 °C. ^{31}P NMR ($CDCl_3$) δ: 37.6. ^1H NMR ($CDCl_3$) δ: 9.18 (s, 1H, Napy-H^5), 8.68 (d, 1H, Napy-H^7, *J* 5.9 Hz), 8.10 (d, 1H, Napy-H^4, *J* 8.4 Hz), 7.98–8.04 (m, 4H, *m*-Ph), 7.78 (d, 1H, Napy-H^8, *J* 5.9 Hz), 7.45–7.49 (m, 6H, *o*-Ph, *p*-Ph), 7.38 (d, 1H, Napy-H^3, *J* 8.4 Hz), 3.30 (d, 2H, CH_2, *J* 8.1 Hz), 1.28 [d, 6H, $(CH_2)_3$, *J* 15.8 Hz].

2-[(2-Diphenylphosphory)heptyl]-1,6-naphthyridine **12**. A white powder. Yield 83%, mp 121–122 °C. ^{31}P NMR ($CDCl_3$) δ: 36.1. ^1H-{^{31}P} NMR ($CDCl_3$) δ: 9.13 (s, 1H, Napy-H^5), 8.71 (d, 1H, Napy-H^7, *J* 5.9 Hz), 7.97 (d, 1H, Napy-H^4, *J* 8.4 Hz), 7.86 (d, 2H, *o*-Ph, *J* 7.0 Hz), 7.81 (d, 1H, Napy-H^8, *J* 5.9 Hz), 7.76 (d, 2H, *o*-Ph, *J* 7.0 Hz), 7.43–7.45 (m, 3H, *p*-Ph, Napy-H^3), 7.18–7.25 (m, 4H, *m*-Ph), 3.44–3.47 (m, 1H, CH–P), 3.39–3.43 (m, 1H, Napy-CH_2), 3.18–3.23 (m, 1H, Napy-CH_2), 1.55–1.75 (m, 2H, CHP–CH_2CH$_2$), 1.01–1.30 [m, 6H, $(CH_2)_3$], 0.66–0.68 (m, 3H, Me).

‡ *Crystallographic data.* Crystals of **7** ($C_{23}H_{21}N_2OP$, M = 372.39) are triclinic, space group $P\bar{1}$, at 100 K: a = 6.642(3), b = 10.301(5) and c = = 14.741(5) Å, α = 76.706(9), β = 79.961(10), γ = 71.955(9)°, V = 927.4(7) Å^3, Z = 2, d_{calc} = 1.333 g cm^{-3}, μ = 0.164 cm^{-1}, $F(000)$ = 392. Intensities of 10385 reflections were measured with a Bruker SMART APEX2 CCD diffractometer [λ(MoKα) = 0.71072 Å, ω-scans, $2\theta < 56°$] and 4456 independent reflections (R_{int} = 0.0372) were used in the further refinement. The structure was solved by direct methods and refined by the full-matrix least-squares technique against F^2 in the anisotropic approximation for non-hydrogen atoms. The positions of hydrogen atoms were calculated, all hydrogen atoms were refined isotropically in riding model with $U_{iso} = 1.5U_{eq}(C_i)$ for methyl groups and $1.2U_{eq}(C_{ii})$ for other atoms, where $U_{eq}(C)$ are the equivalent thermal parameters of atoms to which corresponding H atoms are bound. The refinement converged to wR_2 = = 0.0693 and GOF = 1.007 for all independent reflections and to R_1 = 0.0323 for 2749 observed reflections with $I > 2\sigma(I)$. All calculations were performed using SHELXTL PLUS 5.0.[8]

CCDC 731895 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2009.

intermediate between those for single and double C–C and C–N bonds. This fact together with the planarity of the fragment structure [average deviation of atoms from the least-square plane is 0.01(1) Å] confirms the delocalization of electron density within naphthyridine core. The C(11) atom has an sp^3 hybridization and forms single bonds with all neighbours. The sp^3 hybridization of the C(11) atom allows the mutual rotation of the naphthyridine and phosphorus-containing fragments around C–C and C–P bonds to occur. As a whole, the geometry of the molecule suggests the mutual repulsion of its fragments. Indeed, the torsion angles Napy–C(11)–C(12) (13°) and Napy–C(11)–C(13) (47°), the position of methyl hydrogens (none of them is directed to the Napy) and the staggered conformation of the molecule along the C–P bond confirm this assumption.

Moreover, only weak stacking intermolecular contacts were found in the crystal structure of compound **7**: between two phenyl rings of different molecules (the shortest distance between the mean-plane of one molecule and the C atom of another molecule is 3.56 Å) and between phenyl and Napy fragments (the shortest distance is 3.37 Å).

In summary, the Friedländer synthesis provides an efficient and easy access to 2-(phosphoryl)alkyl-substituted 1,6-naphthyridines. The synthesized naphthyridines are of interest as biologically active compounds and bidentate heterodifunctional ligands. We intend to compare their coordination properties with those of corresponding phosphorus-containing 1,8-naphthyridines.

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Received: 27th May 2009; Com. 09/3341