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The first application of the Friedländer reaction for the synthesis of [1,8]naphthyridine derivatives containing phosphorus

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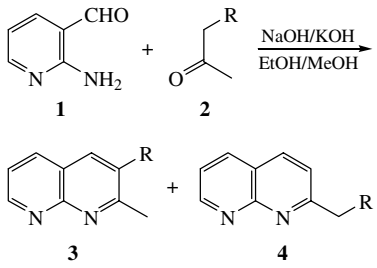
The first 2,3-alkylenesubstituted [1,8]naphthyridines bearing a phosphorus moiety have been synthesised by the Friedländer annulations of 2-aminonicotinaldehyde 1 with 2-diphenylphosphoryl(thiophosphoryl)cyclopentanones 7–9.

Recent publications stimulated a research into the syntheses of functionalised [1,8]naphthyridine derivatives. Valuable products including biologically active substances and ligands for metal complexes have been prepared.[1,2] Unfortunately, phosphorus-containing [1,8]naphthyridines just begin to attract the attention of researchers.[3–6] Taking into account the above, we aimed to elaborate a promising method for the preparation of complicated [1,8]naphthyridine structures possessing additional phosphoalkyl and -alkylene substituents in the 2-position of the heterocyclic nucleus. Incidentally, we employed a version of the Friedländer synthesis based on the interaction between 2-aminonicotinaldehyde **1** and unsymmetrical functionalised alkan-2-ones **2**.[7] This method typically provides substituted [1,8]naphthyridines in high yields under standard hydroxide-catalysed reaction conditions. However, a major drawback is the formation of two regioisomeric products **3** and **4** in the reaction with unsymmetrical ketones (Scheme 1).

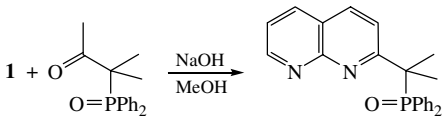


Scheme 1

In the case of R = Alk, the ratio of 2,3-disubstituted **3** to 2-monosubstituted **4** [1,8]naphthyridines is *ca.* 2:1. The use of β-keto phosphonate **2**, R=P(O)(OEt)$_2$, in the synthesis leads to the formation of sole regioisomer **3** (R = H) accompanied by the loss of a phosphonate group.[7]

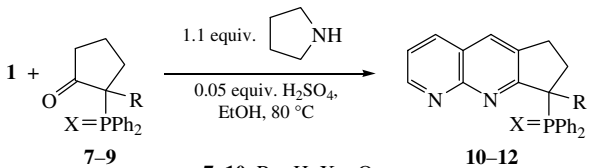
We examined the above reaction using a simple β-keto phosphine oxide, diphenylphosphorylacetone **2**, R = P(O)Ph$_2$,[8] as a substrate. To the best of our knowledge, it is the first example of β-keto phosphine oxide application to the Friedländer naphthyridine synthesis. Aminoaldehyde component **1** is a stable crystalline solid, which is easy to prepare in good yields.[9] Furthermore, the reactivity of **1** under Friedländer conditions had already been demonstrated.[7,10] The process was carried out in MeOH in the presence of aqueous NaOH at room temperature for 24 h (variant A).[7] Reaction yields and selectivities were determined by ^{31}P NMR spectroscopy. As expected, catalysis with hydroxide resulted in high conversion but poor regioselectivity. The ratio of **3**:**4**, R = P(O)Ph$_2$, makes up 3:2 in favour of undesired 2,3-disubstituted naphthyridine **3**. For this reason, to control regioselectivity favouring the formation of 2-substituted product **4**, we employed pyrrolidine instead of NaOH as a new catalyst in highly regioselective Friedländer annulations. Pyrrolidine and its derivatives were found to provide both high conversion and good (≥ 86:14) regioselectivity for 2-alkylsubstituted products **4** in the Friedländer reaction between unmodified methyl ketones and an aromatic aminoaldehyde.[10] We carried out the corresponding interaction of **1** and **2**, R = P(O)Ph$_2$, in EtOH with 1.1 equiv. of pyrrolidine and 0.05 equiv. of H_2SO_4 at 75–80 °C for 24 h (variant B). Unfortunately, in this case, the ratio of **3**:**4**, indicated by ^{31}P NMR spectroscopy, remained almost unchanged. Moreover, the reaction mixture contained 22% unconsumed diphenylphosphorylacetone **2**. Pyrrolidine seems unable to provide high regioselectivity for **4** in the test reaction.

To reach an unequivocal course of the test process, we examined the reaction of a sterically hindered ketone, namely, 1,1-dimethyl-1-diphenylphosphorylacetone **5**,[11] with **1** under conditions of variant A (Scheme 2).



Scheme 2

The interaction proceeds smoothly and provides crystalline product **6** in 72% isolated yield. Further, we studied an analogous reaction of **1** with 2-diphenyl(thio)phosphorylcyclopentanones **7–9** (Scheme 3). This experiment offers the first example of using 2-(thio)phosphorylcycloalkanones in phosphorylated naphthyridine synthesis.



7, **10** R = H, X = O
8, **11** R = Me, X = O
9, **12** R = H, X = S

Scheme 3

As 2-methylcyclopentanone smoothly underwent the Friedländer reaction with **1** at room temperature during 18 h using pyrrolidine as a catalyst, providing the desired naphthyridine in 76%

yield,[9] we carried out the reactions of **1** and 2-substituted cyclopentanones under conditions of variant B. However, ketones **7**–**9** were found much less reactive than 2-methylcyclopentanone and require prolonged aging (36–48 h) at an elevated temperature to drive the reaction to completion. Nevertheless, corresponding 2,3-disubstituted [1,8]naphthyridines **10**–**12** were isolated in moderate (48–63%) yields. Products **10**–**12** are high-melting fine-grained compounds soluble in $CHCl_3$ and EtOH and slightly soluble in other organic solvents. All of the compounds were characterised by melting points, IR, ^{1}H NMR and ^{31}P NMR spectroscopy, mass spectrometry and elemental analyses.†

In conclusion, the Friedländer synthesis provides an efficient and easy access to [1,8]naphthyridines, which are substituted with P=O or P=S group at the α-carbon atom in the 2-position of the heterocyclic nucleus. The compounds prepared are promising tridentate heterodifunctional ligands for the syntheses of coordination systems of new types.

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† NMR spectra were recorded on a Bruker AMX-400 spectrometer at 400.13 (^{1}H) and 161.98 MHz (^{31}P) in $CDCl_3$ solutions using residual signals of the remaining protons of deuterated solvent as an internal standard (^{1}H) and 85% H_3PO_4 (^{31}P) as an external standard. IR spectra were recorded in KBr pellets on a Magna-IR750 (Nicolet) Fourier spectrometer with a 2 cm^{-1} resolution; 128 scans. 2-Diphenylphosphoryl-cyclopentanone **7** and 2-diphenylthiophosphorylcyclopentanone **9** were prepared in accordance with published procedures.[12,13]

2-(1-Diphenylphosphoryl-1-methyl)ethyl[1,8]naphthyridine **6**. A solution of ketone **5** (1.43 g, 5 mmol) and aldehyde **1** (0.61 g, 5 mmol) in ethanol (10 ml) was stirred for 12 h at 20 °C in the presence of 50% aqueous NaOH (1.2 equiv.). The solvent was distilled off, and the crude product was extracted by heptane. After cooling, 1.34 g (72%) of white crystalline **6** was obtained, mp 190–191 °C (decomp.). ^{31}P-{^{1}H} NMR, δ: 38.4. ^{1}H NMR, δ: 1.84 (d, 6H, 2Me, $^3J_{HP}$ 15.0 Hz), 7.30–7.34 (m, 4H, *m*-Ph), 7.39–7.46 (m, 3H, *p*-Ph, naphth-H^6), 7.71–7.76 (m, 4H, *o*-Ph), 8.00–8.04 (m, 2H, naphth-H^3, naphth-H^4), 8.12 (dd, 1H, naphth-H^5, $^1J_{HH}$ 1.8 Hz, $^2J_{HH}$ 4.1 Hz), 9.07 (dd, 1H, naphth-H^7, $^1J_{HH}$ 1.8 Hz, $^2J_{HH}$ 4.1 Hz). Found (%): C, 74.05; H, 5.47; N, 7.40; P, 8.17. Calc. for $C_{23}H_{21}N_2OP$ (%): C, 74.18; H, 5.68; N, 7.52; P, 8.32. IR (KBr, ν/cm^{-1}): 1180 (P=O), 1605, 1110, 760, 730, 710.

2-Diphenylphosphoryl-2-methylcyclopentan-1-one **8**. This product was obtained starting from ketone **7** (3.81 g, 13.4 mmol), MeI (34.2 g, 241 mmol), NaH (60% suspension in oil, 875 mg) and ethanol (150 ml) according to the previously described procedure for 2-diphenylphosphoryl-2-methylcyclohexan-1-one.[14] Yield 1.48 g (50%), mp 97–98 °C. ^{31}P-{^{1}H} NMR, δ: 31.5. ^{1}H NMR, δ: 1.37 (d, 3H, Me, $^3J_{PH}$ 15.8 Hz), 1.73–1.82 (m, 2H, C^{3}H$_2$), 1.89–1.97 (m, 1H, C^{4}H$_2$), 2.03–2.11 (m, 1H, C^{4}H$_2$), 2.23–2.30 (m, 1H, C^{5}H$_2$), 2.70–2.81 (m, 1H, C^{5}H$_2$), 7.40–7.44 (m, 2H, *p*-Ph), 7.49–7.59 (m, 4H, *m*-Ph), 7.78–7.86 (m, 2H, *o*-Ph), 8.09–8.15 (m, 2H, *o*-Ph). Found (%): C, 72.50; H, 6.62; P, 10.58. Calc. for $C_{18}H_{19}O_2P$ (%): C, 72.47; H, 6.42; N, 10.32. IR (KBr, ν/cm^{-1}): 1730 (C=O), 1180 (P=O), 1110, 760, 730, 710.

*8-Diphenylphosphoryl-7,8-dihydro-6*H*-cyclopenta[*b*][1,8]naphthyridine* **10**. A solution of aldehyde **1** (1.22 g, 10 mmol), ketone **7** (2.84 g, 10 mmol), pyrrolidine (0.93 ml, 11.12 mmol) and concentrated H_2SO_4 (0.14 μl, 0.25 mmol) in ethanol (15 ml) was refluxed for 36 h. Then, ethanol was distilled off, and the residue was dissolved in chloroform (50 ml). This solution was washed with water (2×20 ml), dried over K_2CO_3 and evaporated to dryness. A crude product was triturated with diethyl ether. Recrystallization from methylcyclohexane gave **10** as a white solid. Yield 1.78 g (48%), mp 210–211 °C (decomp.). ^{31}P-{^{1}H} NMR, δ: 34.37. ^{1}H NMR, δ: 2.59–2.74 (m, 1H, CH$_2$), 2.84–2.94 (m, 1H, CH$_2$), 3.04–3.12 (m, 1H, CH$_2$), 3.22–3.30 (m, 1H, CH$_2$), 4.54–4.61 (m, 1H, CHP), 7.32–7.43 (m, 4H, *m*-Ph), 7.50–7.64 (m, 4H, *o*-Ph), 7.73–7.80 (m, 2H, *p*-Ph), 7.93 (s, 1H, naphth-H^4), 8.13–8.22 (m, 2H, naphth-H^5, naphth-H^6), 9.06 (dd, 1H, naphth-H^7, $^1J_{HH}$ 1.9 Hz, $^2J_{HH}$ 4.2 Hz). Found (%): C, 74.68; H, 5.22; N, 7.55; P, 7.94. Calc. for $C_{23}H_{19}N_2OP$ (%): C, 74.58; H, 5.17; N, 7.56; P, 8.36. MS, *m*/*z*: 370 [M$^+$]. IR (KBr, ν/cm^{-1}): 1197 (P=O), 1622, 1596, 1558, 1481.

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*8-Diphenylphosphoryl-8-methyl-7,8-dihydro-6*H*-cyclopenta[*b*][1,8]-naphthyridine* **11**. A solution of aldehyde **1** (0.61 g, 5 mmol), ketone **8** (1.48 g, 5 mmol), pyrrolidine (0.46 ml, 5.55 mmol) and concentrated H_2SO_4 (0.14 μl, 0.25 mmol) in ethanol (5 ml) was refluxed for 24 h. Then, the solvent was distilled off, and the residue was dissolved in chloroform (50 ml). This solution was washed with water (2×20 ml), dried over K_2CO_3 and evaporated to dryness. Recrystallization of the residue from heptane gave 1.2 g (63%) of **11** as a pale yellow solid, mp 190–191 °C (decomp.). ^{31}P-{^{1}H} NMR δ: 33.07. ^{1}H NMR, δ: 1.89 (d, 3H, Me, J_{HP} 15.2 Hz), 2.15–2.24 (m, 1H, CH$_2$), 2.51–2.60 (m, 1H, CH$_2$), 2.85–2.91 (m, 1H, CH$_2$), 3.37–3.46 (m, 1H, CH$_2$), 7.11–7.14 (m, 1H, naphth-H^6), 7.29–7.34 (m, 1H, naphth-H^5), 7.47–7.59 (m, 6H, *m*-Ph, *p*-Ph), 7.76 (s, 1H, naphth-H^4), 8.12–8.20 (m, 2H, *o*-Ph), 8.50–8.54 (m, 2H, *o*-Ph), 9.06 (dd, 1H, naphth-H^7, $^1J_{HH}$ 1.9 Hz, $^2J_{HH}$ 4.2 Hz). Found (%): C, 75.05; H, 5.44; N, 7.32; P, 7.95. Calc. for $C_{24}H_{21}N_2OP$ (%): C, 74.99; H, 5.51; N, 7.29; P, 8.06. IR (KBr, ν/cm^{-1}): 1180 (P=O), 1615, 1600.

*8-Diphenylthiophosphoryl-7,8-dihydro-6*H*-cyclopenta[*b*][1,8]naph-thyridine* **12**. A solution of aldehyde **1** (1.22 g, 10 mmol), ketone **9** (3 g, 10 mmol), pyrrolidine (0.93 ml, 11.12 mmol) and concentrated H_2SO_4 (0.28 μl, 0.5 mmol) in ethanol (20 ml) was refluxed for 48 h. A precipitate was filtered off, washed with cold methyl ethyl ketone and diethyl ether. Finally, 2.0 g (52%) of **12** was obtained as a white solid, mp 234–235 °C (from toluene, decomp.). ^{31}P-{^{1}H} NMR, δ: 49.7. ^{1}H NMR, δ: 2.50–2.63 (m, 1H, CH$_2$), 2.70–2.78 (m, 1H, CH$_2$), 2.81–2.96 (m, 1H, CH$_2$), 2.98–3.37 (m, 1H, CH$_2$), 4.71–4.76 (m, 1H, CHP), 7.29–7.41 (m, 4H, *m*-Ph), 7.53 (d, 4H, *o*-Ph, J_{HH} 2.8 Hz), 7.83–7.88 (m, 3H, *p*-Ph, naphth-H^4), 8.04 (d, 1H, naphth-H^5, J_{HH} 4.0 Hz), 8.10–8.27 (m, 1H, naphth-H^6), 9.02 (d, 1H, naphth-H^7, J_{HH} 4.0 Hz). Found (%): C, 71.39; H, 4.95; N, 7.25; P, 7.99; S, 8.28. Calc. for $C_{23}H_{19}N_2PS$ (%): C, 71.48; H, 4.95; N, 7.25; P, 8.01; S, 8.30. MS, *m*/*z*: 386 [M$^+$]. IR (KBr, ν/cm^{-1}): 638 (P=S), 1622, 1597, 1558, 1484.