

AN EFFICIENT SYNTHESIS OF 3-PHOSPHORYLATED 4(1H)-PYRIDONES AND 4-CHLOROPYRIDINES FROM β -ENAMINOPHOSPHONATES

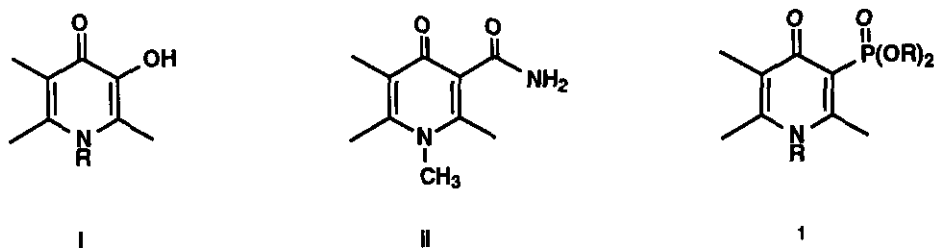
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Abstract- An easy and efficient synthesis of 4(1H)-pyridones (1) substituted with a phosphate group in the 3-position is described. The key step is an addition of β -enaminophosphonates (2) to acylketene (3) generated either from diketene (4) or from the "diketene-acetone adduct", 2,2,6-trimethyl-4H-1,3-dioxin-4-one (5). Subsequent treatment of 4(1H)-pyridones with phosphorus oxychloride in the presence of dimethylformamide afforded the substituted 4-chloropyridine (6).

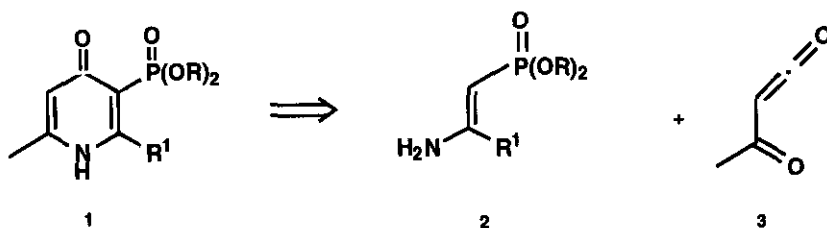
Pyridone ring systems represent an important class of compounds¹ and have attracted an attention in recent years for their biological activities.² 4(1H)-Pyridones constitute the backbone not only of mimosine (I) ($R = \text{CH}_2\text{CH}(\text{NH}_2)\text{COOH}$), a rare amino acid derived from *Mimosa* and *Leucaena* plants^{3a,b} that inhibits the replication of animal cells "in vitro",^{3c,d} but also of modified nucleoside isolated from human urine,⁴ while pyridone (II) is the major metabolite of nicotinamide and nicotinic acid in rats,^{5a} useful as a biological marker to assess the amino acid intake^{5b} and useful for the biotransformation of tryptophan to niacin^{5c} (Scheme 1). Likewise, 4(1H)-pyridones have been used as antiinflammatory^{6a} and antibacterial agents,^{6b} as neuromuscular membrane-permeant antagonists,^{6c} as enzymatic inhibitors^{6d} and for prevention of leucaena toxicosis in cattle.^{6e} Furthermore, 4(1H)-pyridones are key intermediates in the synthesis of oxidopyridinium ylides,^{7a} nucleosides^{7b,c} as well as of semi-synthetic antibiotics with excellent antibacterial activity such as MT 0703^{7d} and KP 736 cephalosporins^{7e} and carbapenems,^{7f,g} while 1,2-dimethyl-3-hydroxy-4(1H)-pyridone (I) ($R = \text{CH}_3$) forms stable chelators with metals^{8a,b} and may find application for the removal of metals from the body in the chelation therapy of aluminium intoxication^{8c,d} and as radiopharmaceuticals.^{8e} Likewise, pyridones are iron chelators suitable for oral administration^{9a} and have been used for both urinary and biliary iron excretion,^{9b} for the treatment of anemias,^{9c} and for the inhibition of tyrosinase.^{9d} In these types of 4(1H)-pyridones the presence of an hydroxy or a carbonyl group in the position 3 (see compounds (I) and (II), Scheme 1) seems to play a key role in the biological activity of these compounds.

Dedicated to Professor Koji Nakanishi on the occasion of his 75th birthday



Scheme 1

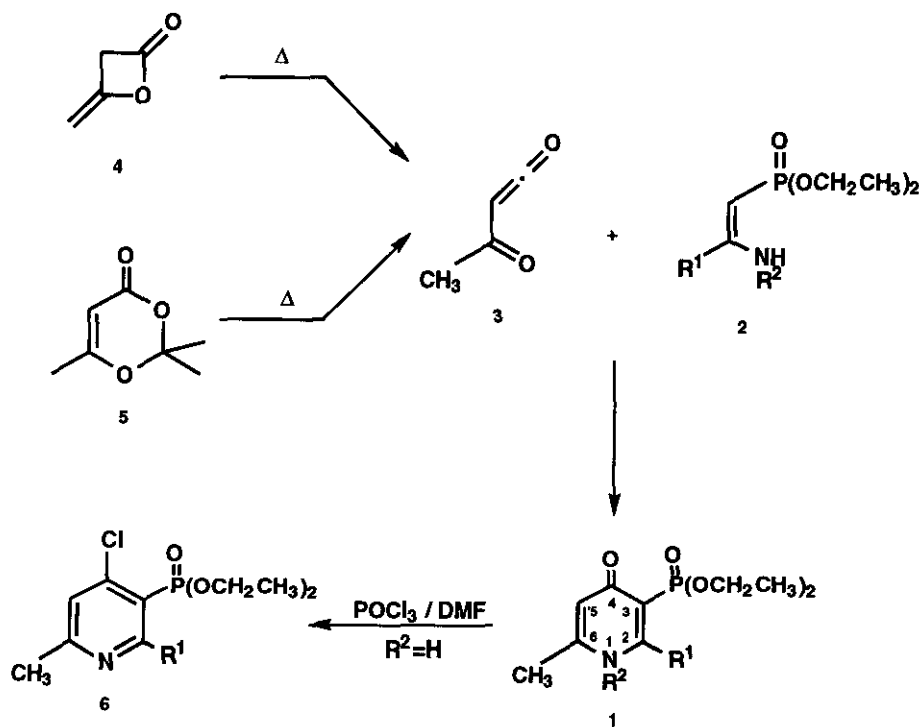
With this in mind, we are interested in the design of new 4(1*H*)-pyridone derivatives substituted with a phosphonate group in the 3 position of the heterocyclic system. This substituent could regulate important biological functions and could increase the biological activity of these type of compounds, in a similar way to that reported for other pharmaceuticals.¹⁰ Classical approaches^{1a} to 4(1*H*)-pyridones involving heterocyclic precursors¹¹ as well as heterocyclization reactions from pentadiyones,^{12a} 1,3,5,-triketones,^{12b} 1,4-dien-3-ones^{12c,d} azirines,^{13a} imines^{13b,c} and enamines,^{6a,13d-e} have been reported. However, to the best of our knowledge, the synthesis of phosphorus substituted 4(1*H*)-pyridones has not been reported. In connection with our interest in the synthesis of five-¹⁴ and six-membered¹⁵ phosphorylated nitrogen heterocycles we have used β -functionalized enamines derived from phosphazenes, phosphonium salts, phosphine oxides and phosphonates as synthetic intermediates in the synthesis of acyclic derivatives such as oximes,^{16a} allylamines,^{16b} hydrazones,^{16c} azadienes,^{16d} aminodienes,^{16e} and β -amino functionalized compounds^{16f,g} as well as phosphorus containing heterocycles.¹⁷ In this context, it is noteworthy that, retrosynthetically, 4(1*H*)-pyridones (**1**) substituted by a phosphonate group in 3-position could be envisaged by reaction of primary enamines (**2**) with acylketene (**3**) (Scheme 2).



Scheme 2

Primary enamines are, however, not stable unless conjugated with an electron-withdrawing group on the β -carbon.¹⁸ In previous papers we have reported a preparation of primary β -enamines derived from phosphazenes¹⁹ and from phosphonates^{15b} and we have used them in the synthesis of cyclic^{15b,17,20} and acyclic^{16g,19} compounds. Continuing with our interest in the synthesis of new phosphorus substituted heterocycles and with the reactivity of functionalized enamines, we report here an easy and high yielding synthesis of 3-phosphonylpyridones (**1**) from primary β -enaminophosphonates (**2**) and acylketenes generated either from diketene (**4**) or from thermolysis of the commercially available and inexpensive 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (**5**).^{21,22}

When primary β -enaminophosphonates ($R^2=H$) (**2**) were allowed to react with an equimolecular amount of diketene (**4**) in toluene at 110°C (7 d) or heating above 100°C in the absence of solvent (12 h), 4(1*H*)-pyridones (**1**) were obtained (see Table 1) in a regioselective fashion (Scheme 3). Compounds (**1**) were characterized on the basis of their spectroscopic data. Thus, in the ^1H -NMR spectrum of compound (**1a**), heterocyclic proton (H-5) of pyridone resonates at $\delta_{\text{H}} = 6.90$ ppm as a well resolved doublet with the long-range coupling constant $^4J_{\text{PH}} = 3.9$ Hz, while the ^{13}C -NMR spectrum of this compound (**1a**) showed absorptions at $\delta_{\text{C}} = 176.5$ ($^2J_{\text{PC}} = 5.5$ Hz) ppm assignable to the carbonyl group, as well as doublets at 159.0 ($^2J_{\text{PC}} = 12.8$ Hz), 115.8 ($^1J_{\text{PC}} = 164.2$ Hz) and 114.3 ($^3J_{\text{PC}} = 9.0$ Hz) for C-2, C-3 and C-5, respectively.



Scheme 3

In order to enhance the scope and the synthetic use of this reaction, the synthesis of pyridone (**1**) derivatives substituted with phosphonic ester groups using synthetic analogues of diketene (**4**) was explored. We chose 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (**5**), the "diketene-acetone adduct", a commercially available and inexpensive reagent.^{21,22} Thermolysis of dioxin-4-one (**5**) above 100°C yields acetylketene and this powerful acetoacetylating agent reacts (12 h) with primary enamines ($R^2=H$) (**2**) affording pyridones (**1**) in excellent yields (see Table 1).

Table 1. 4(1*H*)-Pyridones (**1**) and 4-Chloropyridine (**6**).

Compound	R ¹	R ²	Yield (%)			mp (°C)
1a	<i>p</i> -CH ₃ -C ₆ H ₄	H	88 ^a	91 ^b	90 ^c	267-268
1b		H		87 ^b	92 ^c	265-266
1c		H	71 ^a	84 ^b		248-249
1d		H		88 ^b		240-241
1e		H		86 ^b		242-243
1f					94 ^c	180-181
1g		<i>p</i> -Cl-C ₆ H ₄			81 ^c	210-211
6		-		72 ^d		153-154

^aYield of isolated products (**1**) based on **2** in toluene at 110°C from diketene (**4**). ^bYield of isolated products based on **2** without solvent from diketene (**4**). ^cYield of isolated products based on **2** from dioxin-4-one (**5**). ^dYield of isolated product (**6**) based on **1**.

These results prompted us to extend this reaction and to explore whether secondary enamines with acetylketenes showed a similar reaction pattern leading to new *N*-substituted pyridones (**1**) (R² = aryl) with phosphonic ester groups. Thus, the reaction of enamines (**2**) (R² = aryl) with "diketene-acetone-adduct" (**5**) at 110°C (12 h) yielded *N*-substituted pyridones (**1f,g**) (see Table 1). Spectral data are in agreement with the structure (**1**) and are consistent with previously reported data for compounds (**1a-e**). Therefore, this methodology can be used not only for the preparation of *N*-unsubstituted pyridones (**1a-e**) but also can be applied to the synthesis of *N*-substituted heterocycles (**1f-g**).

On the other hand, 4(1*H*)-pyridones (**1**) are useful intermediates for the preparation of 4-chloropyridines. Treatment of compound (**1b**) with phosphorus oxychloride in dimethylformamide (DMF) and dichloromethane at rt led to the formation of 4-chloropyridine (**6**) (Scheme 3) in excellent yield. Spectroscopic data were in agreement with the assigned structure. MS of **6** showed the molecular ion peak (*m/z*, 339, 40%) as well as M+2 (*m/z*, 341, 14%). To the best of our knowledge, this route

describes the first synthesis of phosphorylated 4-chloropyridines. In this context, it is noteworthy that 4-chloropyridines are key intermediates for the preparation of biologically active compounds such as the benzodiazepine receptor ligand S-8510,^{23a} antibiotics, ^{23b} and complexes with antitumor^{23c} or mutagenic activity. ^{23d}

Table 2. Selected spectral data for the compounds.

Compound	³¹ P-NMR (CD ₃ OD) ^a δ (ppm)	¹ H-NMR (CD ₃ OD) ^a δ (ppm)	¹³ C-NMR (CD ₃ OD) ^a δ (ppm)	IR ^b ν (cm ⁻¹)	MS ^c (m/z)
1a	8.4	0.86 (t, 6H, ³ J _{HH} =6.9 Hz, CH ₃), 2.28 (s, 3H, CH ₃), 2.43 (s, 3H, CH ₃), 3.41 (m, 4H, OCH ₂), 6.91 (d, 1H, ⁴ J _{PH} =3.9 Hz, CH), 7.3 (m, 4H, arom)	16.5 (d, ³ J _{PC} =8.0 Hz, CH ₃), 19.1 (CH ₃), 21.5 (CH ₃), 62.1 (d, ² J _{PC} =6.0 Hz, OCH ₂), 114.3 (d, ³ J _{PC} =9.0 Hz, C-5), 115.8 (d, ¹ J _{PC} =164.2 Hz, C-3), 129.7-130.4 (C-arom), 142.2 (C-ipso arom), 155.4 (C-6), 159.0 (d, ² J _{PC} =12.8 Hz, C-2), 176.2 (d, ² J _{PC} =5.5 Hz, C=O)	3076(NH) 1651(C=O) 1205 (P=O)	335 (M ⁺ , 30%)
1b	8.5	0.80 (t, 6H, ³ J _{HH} =7.1 Hz, CH ₃), 2.38 (s, 3H, CH ₃), 3.34 (m, 4H, OCH ₂), 6.87 (d, 1H, ⁴ J _{PH} =3.8 Hz, CH), 7.32-7.43 (m, 5H, arom)	16.5 (d, ³ J _{PC} =7.6 Hz, CH ₃), 19.2 (CH ₃), 62.1 (d, ² J _{PC} =5.5 Hz, OCH ₂), 114.3 (d, ³ J _{PC} =8.6 Hz, C-5), 115.8 (d, ¹ J _{PC} =166.2 Hz, C-3), 129.1-130.5 (C-arom), 134.4 (C-ipso arom), 155.6 (C-6), 158.8 (d, ² J _{PC} =12.6 Hz, C-2), 176.1 (d, ² J _{PC} =5.5 Hz, C=O)	3092 (NH) 1648 (C=O) 1211 (P=O)	321 (M ⁺ , 35%)
1c	8.2	0.90 (t, 6H, ³ J _{HH} =7.0 Hz, CH ₃), 2.45 (s, 3H, CH ₃), 3.58 (m, 4H, OCH ₂), 6.54-7.86 (m, 3H, arom), 6.80 (d, 1H, ⁴ J _{PH} =3.4 Hz, CH)	16.4 (d, ³ J _{PC} =7.1 Hz, CH ₃), 19.4 (CH ₃), 62.5 (d, ² J _{PC} =5.6 Hz, OCH ₂), 112.0 (d, ¹ J _{PC} =159.6 Hz, C-3), 114.1 (d, ³ J _{PC} =8.1 Hz, C-5), 114.2-147.7 (C-arom), 145.1 (C-ipso arom), 146.5 (d, ² J _{PC} =10.6 Hz, C-2), 156.0 (C-6), 176.5 (d, ² J _{PC} =4.6 Hz, C=O)	3151 (NH) 1647 (C=O) 1206 (P=O)	311 (M ⁺ , 100%)
1d	8.2	0.88 (t, 6H, ³ J _{HH} =7.0 Hz, CH ₃), 2.41 (s, 3H, CH ₃), 3.48 (m, 4H, OCH ₂), 6.88 (d, 1H, ⁴ J _{PH} =3.5 Hz, CH), 7.0-7.6 (m, 3H, arom)	16.6 (d, ³ J _{PC} =7.6 Hz, CH ₃), 19.2 (CH ₃), 62.3 (d, ² J _{PC} =5.9 Hz, OCH ₂), 114.7 (d, ³ J _{PC} =8.6 Hz, C-5), 116.8 (d, ¹ J _{PC} =163.2 Hz, C-3), 128.2-133.9 (C-arom), 132.7 (C-ipso arom), 152.3 (d, ² J _{PC} =11.6 Hz, C-2), 156.1 (C-6), 176.1 (d, ² J _{PC} =5.1 Hz, C=O)	3129 (NH) 1645 (C=O) 1229 (P=O)	327 (M ⁺ , 100%)
1e	7.9	0.84 (t, 6H, ³ J _{HH} =6.9 Hz, CH ₃), 2.48 (s, 3H, CH ₃), 3.47 (m, 4H, OCH ₂), 7.00 (d, 1H, ⁴ J _{PH} =3.8 Hz, CH), 7.5-8.6 (m, 5H, arom)	16.4 (d, ³ J _{PC} =7.6 Hz, CH ₃), 19.5 (CH ₃), 62.2 (d, ² J _{PC} =5.5 Hz, OCH ₂), 114.9 (d, ³ J _{PC} =8.1 Hz, C-5), 115.7 (d, ¹ J _{PC} =161.6 Hz, C-3), 126.8-150.2 (C-arom), 151.9 (C-ipso arom), 156.0 (d, ² J _{PC} =12.6 Hz, C-2), 156.5 (C-6), 176.0 (d, ² J _{PC} =6.0 Hz, C=O)	3084 (NH) 1642 (C=O) 1217 (P=O)	322 (M ⁺ , 42%)

Table 2. (continuation)

Compound	³¹ P-NMR (CDCl ₃) ^a δ (ppm)	¹ H-NMR (CDCl ₃) ^a δ (ppm)	¹³ C-NMR (CDCl ₃) ^a δ (ppm)	IR ^b ν (cm ⁻¹)	MS ^c (m/z)
1f	15.4	1.09 (t, 6H, ³ J _{HH} =7.1 Hz, CH ₃), 1.91 (s, 3H, CH ₃), 3.89 (m, 2H, OCH ₂), 4.06 (m, 2H, OCH ₂), 6.41 (d, 1H, ⁴ J _{PH} =5.9 Hz, CH), 6.93-7.21 (m, 10H, arom)	16.1 (d, ³ J _{PC} =6.5 Hz, CH ₃), 21.8 (CH ₃), 61.8 (d, ² J _{PC} =6.0 Hz, OCH ₂), 117.4 (d, ¹ J _{PC} =194.9 Hz, C-3), 119.2 (d, ³ J _{PC} =9.0 Hz, C-5), 127.0-129.2 (C-arom), 134.5 (C-ipso arom), 139.3 (C-ipso arom), 148.7 (C-6), 157.5 (d, ² J _{PC} =18.1 Hz, C-2), 178.2 (d, ² J _{PC} =4.0 Hz, C=O)	3051 (NH) 1635 (C=O) 1246 (P=O)	397 (M ⁺ , 5%)
1g	15.0	1.44 (t, 6H, ³ J _{HH} =7.0 Hz, CH ₃), 2.27 (s, 3H, CH ₃), 4.24 (m, 2H, OCH ₂), 4.38 (m, 2H, OCH ₂), 6.76 (d, 1H, ⁴ J _{PH} =6.3 Hz, CH), 7.23-7.89 (m, 9H, arom)	16.1 (d, ³ J _{PC} =6.0 Hz, CH ₃), 21.9 (CH ₃), 61.9 (d, ² J _{PC} =6.0 Hz, OCH ₂), 117.7 (d, ¹ J _{PC} =195.9 Hz, C-3), 119.3 (d, ³ J _{PC} =9.1 Hz, C-5), 127.3-130.5 (C-arom), 134.2 (C-ipso arom), 134.8 (C-ipso arom), 137.8 (C-ipso arom), 148.5 (C-6), 157.4 (d, ² J _{PC} =18.6 Hz, C-2), 178.1 (d, ² J _{PC} =4.0 Hz, C=O)	3068 (NH) 1642 (C=O) 1238 (P=O)	431 (M ⁺ , 15%)
6	12.9	1.10 (t, 6H, ³ J _{HH} =7.0 Hz, CH ₃), 2.59 (s, 3H, CH ₃), 3.80 (m, 2H, OCH ₂), 3.96 (m, 2H, OCH ₂), 7.27 (d, 1H, ⁴ J _{PH} =3.3 Hz, CH), 7.41-7.59 (m, 5H, arom)	15.9 (d, ³ J _{PC} =7.0 Hz, CH ₃), 24.3 (CH ₃), 62.2 (d, ² J _{PC} =6.0 Hz, OCH ₂), 119.5 (d, ¹ J _{PC} =195.9 Hz, C-3), 123.5 (d, ³ J _{PC} =7.5 Hz, C-5), 127.7-128.9 (C-arom), 141.8 (C-ipso arom), 148.8 (d, ² J _{PC} =3.0 Hz, C-4), 161.0 (C-6), 164.5 (d, ² J _{PC} =9.6 Hz, C-2)	1255 (P=O)	339 (M ⁺ , 40%)

^a Obtained on a Varian VXR 300 Spectrometer. ^b Recorded in a Nicolet FTIR Magna 550. ^c Obtained on a Hewlett Packard 5890 Spectrometer.

In conclusion, the synthesis described here provides an efficient and easy access to 4(1H)-pyridones (1) and 4-chloropyridine (6) substituted with a phosphonate group in 3-position, making use of readily available starting materials. 4-(1H)-Pyridones and 4-chloropyridines are useful compounds in medicinal chemistry since these products display a broad range of biological activities and have been widely used as pharmaceuticals.^{3-9,23}

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