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Synthesis of Diethyl Pyridin-2-ylphosphonates and Quinolin-2-ylphosphonates by Deoxygenative Phosphorylation of the Corresponding *N*-Oxides

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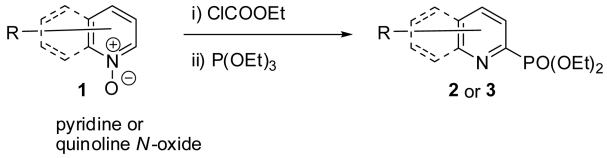
Dialkyl pyridin-2-ylphosphonates widely used as corrosion inhibitors, dispersing and emulsifying agents, antistatics and lubricant additives in various technological fields[1] are known as potent insecticides,[2] fungicides[3] and herbicides.[4] Pyridin-2-ylphosphonates have also been reported to have a promising cytokinin activity,[5] anti-proliferating and anti-platelet activating factor (anti-PAF) activities,[6] and to be used as a chelate ligand to prepare various metal-organic frameworks, such as polymeric material with Zn, Cd and Ag showing luminescence properties, iron complex as a catalyst and copper complex with weak ferromagnetism.[7] Because biological properties of dialkyl pyridin-2-ylphosphonates and physical properties of their complexes depend both on the phosphorus-containing ligand, simple and efficient synthetic approaches of them are necessary.

There are only a few reports for the preparation of dialkyl pyridin-2-ylphosphonates. The first and most general approach developed by Redmore[1,8] consists of the reaction of *N*-methoxypyridinium salts with sodium dialkyl phosphites in the corresponding dialkyl phosphite solvent keeping temperature below −15 °C. Unfortunately, the reactions are highly sensitive and usually give the desired products in low to moderate yield, partly due to decomposition of the reactants under the reaction condition. The nucleophilic substitution approach of pyridine halide with sodium dialkyl phosphite[9] and with triethyl phosphite,[10] are even less efficient and require harsh reaction conditions. The third synthetic protocol of dialkyl pyridin-2-ylphosphonates using *N*-trifluoromethane sulphonyl pyridinium triflate and trialkyl phosphites suffers from a rather lengthy method with low overall yields.[11] The most recent approach is the palladium catalyzed cross coupling reaction of pyridyl halide with triethyl phosphite, which also have limitation due to the availability of substrates and low yield.[12]

While all of these methods are useful in its own right, each suffers from one or more limitations including a lack of generality, the use of excess amount of toxic reagents, or the need to employ harsh reaction condition.

As a result of an ongoing research of heteroaromatics and their *N*-oxides,[13] we are going to report a simple and efficient regioselective approach for the preparation of the corresponding diethyl pyridin-2-ylphosphonates and diethyl quinolin-2-ylphosphonates from the pyridine *N*-oxides and quinoline *N*-oxides by the activation of *N*-oxides with ethyl chloroformate followed by the treatment with triethyl phosphite (Scheme 1). The application of our method for the regioselective synthesis of the isoquinolinyl-1-phosphonates from two isoquinoline *N*-oxides also show the excellent result.

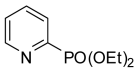
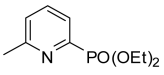
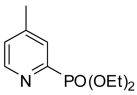
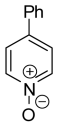
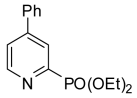
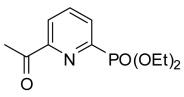
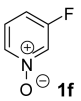
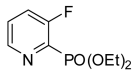
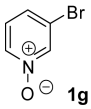
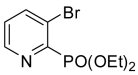
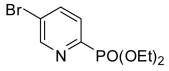


Scheme 1

A study on the amount of ethyl chloroformate and triethyl phosphite used for the reaction showed that the optimum amount of ethyl chloroformate and triethyl phosphite was 3 eq.. To a solution of pyridine *N*-oxide (200 mg, 2.1 mmol) in methylene chloride (10 mL) at rt under argon atmosphere was added ethyl chloroformate (3 eq.) and then triethyl phosphite (3 eq.). After reaction for 30 min and purification, a diethyl pyridin-2-ylphosphonate was obtained in 94.2% isolated yield. The pyridine *N*-oxide derivatives with electron donating group (entries 2-4, Table 1) and electron withdrawing group (entry 5, Table 1) at 2 or 4 position under optimum condition underwent regioselective deoxygenative phosphorylation to give the corresponding pyridin-2-ylphosphonate as a product in good to high yields. The reaction of pyridine *N*-oxide with fluoro functional group at 3 position under the reaction condition gave 2-phosphorylated regioisomer **2f** as a product selectively and the reason of selectivity is not clear. The reaction of pyridine *N*-oxide with bromo functional group at 3 position (entries 7, Table 1) give a mixture of two isomers with regioisomer **2g** as a major product.

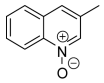
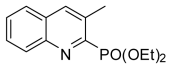
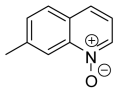
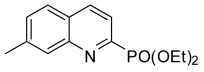
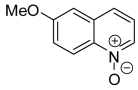
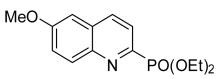
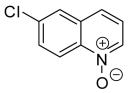
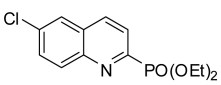
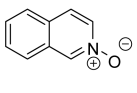
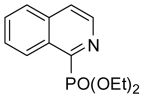
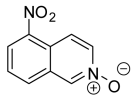
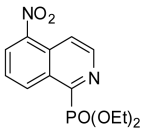
Our protocol was expanded to the reaction of quinoline *N*-oxides and isoquinoline *N*-oxides. The reactions of electron sufficient and deficient quinoline *N*-oxides (entries 1-4, Table 2) as well as two isoquinoline *N*-oxides (entries 5 and 6, Table 2) under our condition also underwent deoxygenative phosphorylation regioselectively to afford the corresponding diethyl quinolin-2-ylphosphonate and diethyl isoquinolin-1-ylphosphonate respectively in good to high respective yields.

Table 1. Deoxygenative phosphorylation of pyridine *N*-oxide

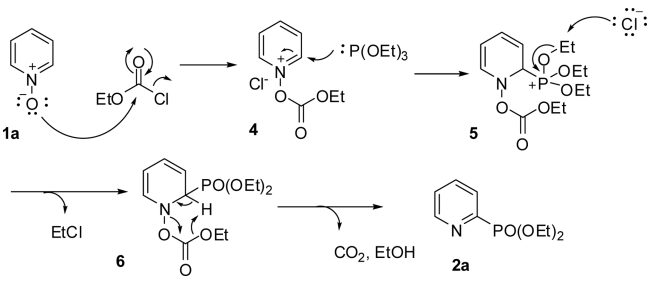
Entry	Substrate	Product/Yield (%)[b]	
1	 **1a**	 **2a** (94.2)	
2	 **1b**	 **2b** (84.8)	
3	 **1c**	 **2c** (91.0)	
4	 **1d**	 **2d** (89.6)	
5	 **1e**	 **2e** (72.0)	
6	 **1f**	 **2f** (84.5)	
7	 **1g**	 **2g** (43.9)	 **3g** (37.3)

[a]All reactions were carried out using $P(OEt)_3$ (3 equiv.) and ethyl chloroformate (3 equiv.) in methylene chloride at r.t for 30 min. [b]Isolated yield.

Table 2. Deoxygenative phosphorylation of quinoline and isoquinoline *N*-oxide

Entry	Substrate	Product	Yield (%)[b]
1	 **1h**	 **2h**	78.3
2	 **1i**	 **2i**	86.2
3	 **1j**	 **2j**	75.7
4	 **1k**	 **2k**	97.8
5	 **1l**	 **2l**	88.2
6	 **1m**	 **2m**	86.4

[a]All reactions were carried out using $P(OEt)_3$ (3 equiv.) and ethyl chloroformate (3 equiv.) in methylene chloride at rt for 30 min. [b]Isolated yield.



Scheme 2

The reaction of a pyridine *N*-oxide **1a** as an example seems to proceed as follows (Scheme 2). The oxygen of *N*-oxide was ethoxycarbonylated by the reaction with ethyl chloroformate to give a pyridinium salt **4**, which was attacked by triethyl phosphite followed by Arbuzov reaction to provide intermediate **6**, which undergo decarboxylation and intramolecular dehydrogenation to give the final product **2a**.

In conclusion, the reaction of pyridine *N*-oxide and quinoline *N*-oxide activated by ethyl chloroformate with triethyl phosphite at rt gave the corresponding diethyl pyridin-2-ylphosphonate and diethyl quinolin-2-ylphosphonate regioselectively in good to excellent yield through oxygenative phosphorylation. The reaction condition is mild and efficient compared to the reported methods.

All chemicals including commercially available pyridine *N*-oxides were purchased from specialized suppliers with analytical purity and used without further purification. Non commercially available pyridine *N*-oxide for the reaction were prepared by known method.[14] IR spectra of products were recorded on a Perkin-Elmer FT-IR 240-c spectrometer using KBr disks. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Bruker 300 spectrometer in $CDCl_3$. High-resolution ESI-MS spectra were obtained on an IT-TOF (Shimadzu, Japan) at Korea Basic Science Institute (KBSI). Column chromatography was performed using Merck silica gel (230–400 mesh). Some known products have physical, spectroscopic, and analytic data identical to those (shown as a CAS registry number) given in the literature.

A Typical Experimental Procedure of Deoxygenative Phosphorylation. To a solution of pyridine *N*-oxide (200 mg, 2.1 mmol) in anhydrous methylene chloride (10 mL) under argon atmosphere was added ethyl chloroformate (0.6 mL, 3 eq.) and the solution was stirred for 10 min at rt. And then triethyl phosphite (1.09 mL, 3 eq.) was added dropwise to the reaction solution. The resulting solution was stirred

for 30 min at rt, diluted with 20 mL of methylene chloride and washed with saturated $NaHCO_3$ (30 mL), water (30 mL × 2) and brine (30 mL). The organic layer was dried with anhydrous $MgSO_4$ and chromatographed on silica gel using ethyl acetate to give diethyl pyridin-2-ylphosphonate **2a** in 94.2% isolated yield.

Diethyl Pyridin-2-ylphosphonate[8a] 2a: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.80 (d, J = 4.5 Hz, 1H), 7.97 (t, J = 6.3 Hz, 1H), 7.80 (q, J = 7.8 Hz, 1H), 7.42 (m, 1H), 4.30-4.16 (m, J = 7.5 Hz, 4H), 1.35 (t, J = 7.2 Hz, 6H).

Diethyl 6-Methylpyridin-2-ylphosphonate[8a] 2b: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (t, J = 7.5 Hz, 1H), 7.65 (t of d, J = 7.8 Hz, J = 6 Hz, 1H), 7.25 (d, J = 7.8 Hz, 1H), 4.26-4.18 (m, J = 7.2 Hz, 4H), 2.61 (s, 3H), 1.34 (t, J = 6.6 Hz, 6H).

Diethyl 4-Methylpyridin-2-ylphosphonate[8a] 2c: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.57 (d, J = 5.1 Hz, 1H), 7.75 (d, J = 7.2 Hz, 1H), 7.18-7.18 (m, 1H), 4.25-4.12 (m, 4H), 2.34 (s, 3H), 1.28 (t, J = 7.5 Hz, 6H).

Diethyl 4-Phenylpyridin-2-ylphosphonate[15(a)] 2d: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.82 (d, J = 4.2 Hz, 1H), 8.21 (dd, J = 7.5 Hz, J =1.61 Hz, 1H), 7.68-7.61 (m, 3H), 7.52-7.44 (m, 3H), 4.32-4.18 (m, 4H), 1.36 (t, J = 6.9 Hz, 6H).

Diethyl 6-Acetylpyridin-2-ylphosphonate[15(b)] 2e: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16-8.06 (m, 2H), 7.98 (t of d, J = 7.5 Hz, J = 5.4 Hz, 1H), 4.30 (m, 4H), 1.39 (t, J = 6.3 Hz, 6H).

Diethyl 3-Fluoropyridin-2ylphosphonate[15(c)] 2f: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.58-8.57 (m, 1H), 7.50-7.44 (m, 2H), 4.34-4.24 (m, 4H), 1.37 (t of d, J = 7.5 Hz, J = 3 Hz, 6H).

Diethyl 3-Bromopyridin-2-ylphosphonate[15(d)] 2g: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.85 (d, J = 1.2 Hz, 1H), 7.97-7.92 (m, 1H), 7.86 (t, J = 6 Hz, 1H), 4.26-4.18 (m, 4H), 1.34 (t, J = 7.2 Hz, 6H).

Diethyl 5-Bromopyridin-2-ylphosphonate[15(e)] 3g: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.68 (d, J = 4.2 Hz, 1H), 7.97 (t, J = 7.2 Hz, 1H), 7.30-7.26 (m, 1H), 4.36-4.26 (m, 4H), 1.40 (t, J = 6 Hz, 6H).

Diethyl 3-Methylquinolin-2-ylphosphonate 2h: Light yellow syrup. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (d, J = 8.4 Hz, 1H), 7.97 (t, J = 6.6 Hz, 1H), 7.76 (d, J = 8.7 Hz, 1H), 7.68 (t of d, J = 6.9 Hz, J = 1.8 Hz, 1H), 7.56 (t, J = 7.8 Hz, 1H), 4.41-4.28 (m, 4H), 2.77 (s, 3H), 1.42 (t, J = 7.5 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.4 (d, J = 222 Hz), 146.4 (d, J = 26.3 Hz), 136.8 (d, J = 12 Hz), 133.4 (d, J = 27.8 Hz), 130.2 (s), 128.7 (d, J = 49.5 Hz), 128.7 (d, J = 5.3 Hz), 126.8 (d, J = 1.5 Hz), 63.1 (d, J = 2.3 Hz), 19.6 (s), 16.4 (d, J = 6.8 Hz). IR (film): 1234 cm^{-1} (P=O). HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{14}H_{18}NO_3PNa$: 302.0922; found: 302.0923.

Diethyl 7-Methylquinolin-2-ylphosphonate 2i: Colorless syrup. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (dd, J = 8.4 Hz, J = 6 Hz, 1H), 8.02 (s, 1H), 7.92 (dd, J = 8.1Hz, J = 4.8 Hz, 1H), 7.73 (d, J = 8.7 Hz, 1H), 7.45 (d, J = 8.4 Hz, 1H), 4.35-4.22 (m, 4H), 2.56 (s, 3H), 1.36 (t, J = 6.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.6 (d, J = 224.3 Hz), 148.5 (d, J =26.3 Hz), 140.6 (s), 135.8 (d, J = 12 Hz), 130.69 (s), 129.3 (s), 127.3 (d, J = 1.5 Hz), 126.7 (d, J = 3.8 Hz), 122.7 (d, J = 26.3 Hz), 63.1 (d, J = 6 Hz), 22.2 (d, J = 53.3 Hz), 16.4 (d, J = 6 Hz). IR (film): 1250 cm^{-1} (P=O). HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{14}H_{18}NO_3PNa$: 302.0922; found : 302.0920.

Diethyl 6-Methoxyquinolin-2-ylphosphonate 2j: Light yellow solid. mp 78-79 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15-8.10 (m, J = 9.3 Hz, 2H), 7.94 (dd, J = 8.1 Hz, J = 5.1 Hz, 1H), 7.41 (dd, J = 9.3 Hz, J = 2.4 Hz, 1H), 7.07 (d, J = 3 Hz, 1H), 4.28 (m, J = 6.9 Hz, 4H), 3.95 (s, 1H), 1.36 (t, J = 6.9 Hz, 6H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1 (s), 149.6 (d, J = 225.8 Hz), 144.6 (d, J = 26.1 Hz), 134.5 (d, J = 11.9 Hz), 131.9 (d, J = 1.1 Hz), 130.0 (d, J = 3.3 Hz), 123.8 (d, J = 26.7 Hz), 123.3 (s), 104.6 (d, J = 1.6 Hz), 63.0 (d, J = 5.9 Hz), 55.6 (s) 16.3 (d, J = 6.1 Hz). IR (film): 1247 cm^{-1} (P=O). HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{14}H_{18}NO_4PNa$: 318.0871; found: 318.0869.

Diethyl 6-Chloroquinolin-2-ylphosphonate 2k: Light yellow solid. mp 46-47 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (d, J = 8.4 Hz, 1H), 8.17 (d, J = 7.5 Hz, 1H), 8.00 (dd, J = 8.4 Hz, J = 4.8 Hz, 1H), 7.84 (d, J = 2.4 Hz, 1H), 7.70 (dd, J = 8.4 Hz, J = 2.4 Hz, 1H), 4.36-4.24 (m, 4H), 1.38 (t, J = 6.6 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.1 (d, J = 224.3 Hz), 146.5 (d, J = 26.3 Hz), 135.3 (d, J = 12 Hz), 134.3 (s), 132.0 (s), 131.2 (s), 129.1 (d, J = 3.8 Hz), 126.3 (d, J = 1.5 Hz), 124.1 (d, J = 26.3 Hz), 63.3 (d, J = 6 Hz), 58.2 (s), 16.4 (d, J = 6 Hz). IR (film): 1234 cm^{-1} (P=O). HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{13}H_{15}NO_3ClPNa$: 322.0376; found: 322.0376.

Diethyl Isoquinolin-1-ylphosphonate[1] 2l: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.96 (d, J = 7.8 Hz, 1H), 8.70 (d, J = 5.1 Hz, 1H), 7.87 (d, J = 7.5 Hz, 1H), 7.81-7.69 (m, 3H), 4.34-4.29 (m, 4H), 1.38 (t, J = 6.6 Hz, 6H).

Diethyl 5-Nitroisoquinolin-1-ylphosphonate 2m: Yellow syrup. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.41 (d, J = 8.7 Hz, 1H), 8.91 (d, J = 6.0 Hz, 1H), 8.59 (dd, J = 6.0 Hz, J = 2.7 Hz, 1H), 8.54 (d, J = 6.6 Hz, 1H), 7.80 (t, J = 7.8 Hz, 1H), 4.38-4.28 (m, 4H), 1.39 (t, J = 6.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.7 (d, J = 230.6 Hz), 145.2 (d, J = 3.8 Hz), 144.9 (d, J = 24.5 Hz), 134.2 (s), 129.9 (d, J = 30.2 Hz), 128.4 (d, J = 11.3 Hz), 128.2 (s), 126.7 (d, J = 0.8 Hz), 118.3 (d, J = 4.3 Hz), 63.7 (d, J = 6.5 Hz), 16.2 (d, J = 6.2 Hz). IR (film): 1254 cm^{-1} (P=O). HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{13}H_{15}N_2O_5PNa$: 333.0616; found: 333.0615.

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