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SYNTHESIS OF NITROGEN BRIDGEHEAD HETEROCYCLES WITH PHOSPHONATES VIA A NOVEL TANDEM PROCESS

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Abstract – A novel and efficient method was developed for the synthesis of nitrogen bridgehead heterocycles with phosphonates. Nitrogen containing five-membered heterocyclic aldehyde and diethyl 3-bromoprop-1-enylphosphonate were used as substrates. Bridgehead nitrogen-containing arylphosphonates were obtained via one-pot reaction including four steps: S_N2, deprotonation followed by electron flow, nucleophic additon and elimination of water.

INTRODUCTION

The importance of arylphosphonates in organic synthesis,[1] materials,[2] and medicinal chemistry[3] has been well documented for years. They are used, e.g., in the synthesis of heterocyclic compounds,[4] designing fuel cell membranes,[5] materials with special optical properties,[6] and building blocks in polymer sciences.[7] There also has been a growing interest in these compounds in medicinal chemistry and nucleic acid chemistry due to biological activity such as inhibitors of farnesyl protein transferase,[8] progesterone receptor antagonists[3b] and antiviral activity.[9] Thus, the creation of new arylphosphonates could have a great impact on various fields of chemical science.[10]

Bridgehead nitrogen-containing heterocycles are an important class of compounds due to their presence in natural and non-natural products, which exhibit useful biological activities.[11] Among such compounds,

indolizine, pyrido[1,2-*a*]benzimidazole and pyrazolo[1,5-*a*]pyridine are particularly interesting because of their similarities and diversions in structure to indole.[12] Synthetic indolizines can be used as calcium entry blockers,[13] potential central nervous system depressants,[14] 5-HT3 receptor antagonist,[15] histamine H3 receptor antagonists,[16] cardiovascular agents,[17] and PLA2 inhibitors.[18] They have also drawn much attention owing to their possible usage as dyes and chemosensors.[19] Pyrido[1,2-*a*]benzimidazoles receive much more attention because of their pharmaceutical applications as antifungal agents,[20] antiviral agents[21] and antineoplastic agents.[22] Furthermore, some of them also exhibit unique fluorescent properties and potential application in electroluminescence (EL) materials.[23] Pyrazolo[1,5-*a*]pyridines display numerous biological activities and pharmacological properties. For instance, some of them are used as dopamine D2-like receptor antagonist in the treatment of neurological disorders.[24] Some derivatives are synthesized as adenosine A1 receptor antagonists[25] and CRF1 receptor antagonist.[26] Additionally, they are also useful for the treatment of rheumatoid arthritis[27] and herpes viral infection.[28]

Despite continued interest in these building blocks, synthetic methods in the literatures suffer strict operation conditions or low yields.[29] As far as we know, there remain no general synthetic routes to form these nitrogen bridgehead heterocycles.

Due to the synthetic and practical importance of arylphosphonate derivatives and bridgehead nitrogen-containing heterocycles, we are especially interested to extend the previously found tandem reaction[30] to synthesize the nitrogen bridgehead heterocycles with phosphonate. Here, we report a convenient, transition metal-free and general method for the synthesis of indolizine, pyrido[1,2-*a*]benzimidazole and pyrazolo[1,5-*a*]pyridine phosphonates. Pyrrole-2-carbaldehyde (benzimidazole carbaldehyde or pyrazole carbaldehyde) and diethyl 3-bromoprop-1-enylphosphonate were used as substrates, potassium carbonate as the base, and DMF as the solvent in one-pot.

RESULTS AND DISCUSSION

The reaction conditions were optimized by using 4-propionyl-1*H*-pyrrole-2-carbaldehyde **1a** and diethyl 3-bromoprop-1-enylphosphonate **2** as the model substrates, and K_2CO_3 in DMF was found to be the most efficient system (Table 1). It was started by screening various bases in DMF, and K_2CO_3 provided the highest yield (Table 1 entries 1-6). Then the effect of solvents was investigated, and DMF was proved to be the most efficient solvent (entries 7-11). The reaction was also carried out with NaH as the base and MeCN as the solvent, but yield of the product was much lower. Yields of **3a** under other conditions were similar (entries 1, 3, 7, 11). Consequently, all following reactions were conducted with K_2CO_3 in DMF.

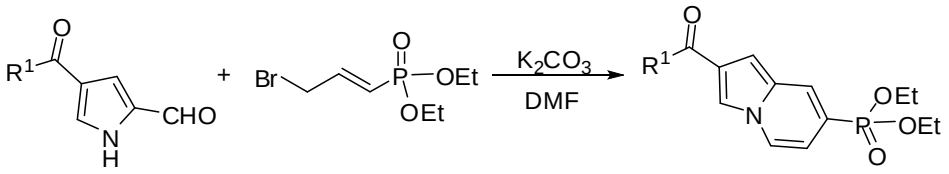
To explore the scope of this methodology, a variety of pyrrole-2-carbaldehyde were studied under the reaction conditions which were optimized above. As observed in Table 2, a series of indolizine phosphonates **3a-g** were obtained in moderate to good yields under mild conditions. We tried aliphatic

substituent ethyl and a variety of phenyl to investigate the effect of R^1 on the yield. When R^1 was 4-fluorophenyl, the lowest yield of 65% was obtained. When R^1 was ethyl, 4-methoxyphenyl, 4-chlorophenyl or 4-nitrophenyl, we got analogously good yield, no matter the substituent attached to phenyl was electron-drawing or electron-donating. Thus, the yield was hardly dependent on the substituent R^1.

Table 1. Solvent and base effects on the novel tandem reaction

Entry	Base	Solvent	Time (h)	Isolated Yield (%)
1	K_2CO_3	DMF	8	84
2	$KHCO_3$	DMF	60	0
3	Na_2CO_3	DMF	6	61
4	NaOH	DMF	0.5	22
5	MgO	DMF	60	0
6	Et_3N	DMF	60	0
7	K_2CO_3	MeCN	16	75
8	K_2CO_3	acetone	16	63
9	K_2CO_3	DCM	60	0
10	K_2CO_3	THF	60	53
11	K_2CO_3	EtOH	16	73

Table 2. Synthesis of Indolizine Phosphonates



1 **2** **3**

Entry	R^1	Product	Isolated Yield (%)
1	ethyl	**3a**	84
2	phenyl	**3b**	74
3	4-methylphenyl	**3c**	66
4	4-methoxyphenyl	**3d**	82
5	4-chlorophenyl	**3e**	83
6	4-fluorophenyl	**3f**	65
7	4-nitrophenyl	**3g**	80

The structures of adducts **3a-g** were characterized by spectroscopic methods (^{1}H and ^{13}CNMR, IR, and MS). The structure of **3g** was further confirmed by X-ray crystallographic analysis as shown in Figure 1.

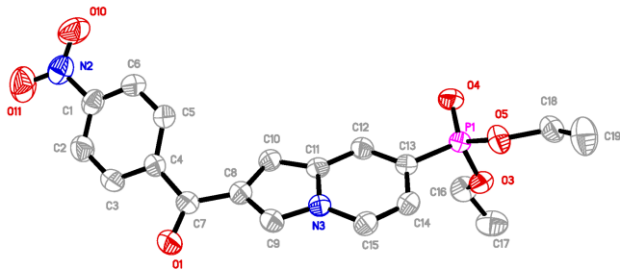
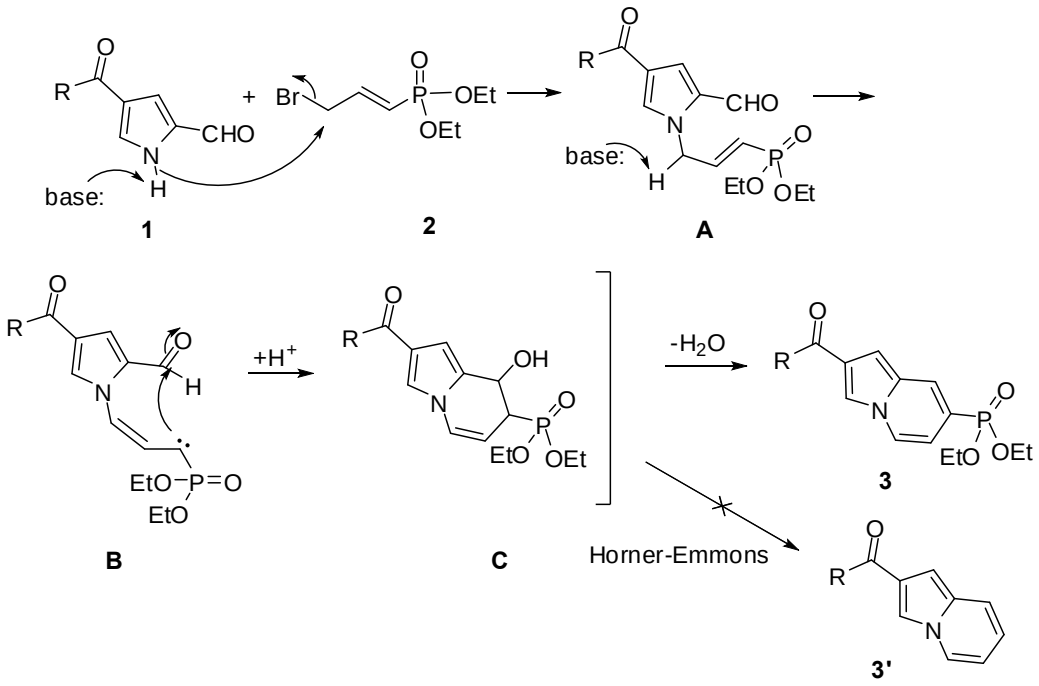


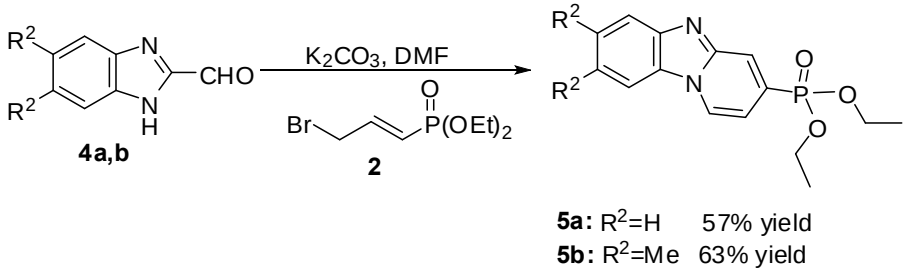
Figure 1. Crystal structure of **3g**

On the basis of the structures of the products, we propose a plausible reaction course for the one-pot tandem reaction (Scheme 1). The first step is the formation of the intermediate **A** through an intermolecular S_N2 reaction between pyrrole-2-carbaldehyde **1** and diethyl 3-bromoprop-1-enylphosphonate **2**. The second step is initiated by deprotonation of the intermediate **A**, and then a series of electron flow makes the intermediate **B** formed. The third step is an intramolecular nucleophilic addition between the formed β,γ-unsaturated α-carbanion of ester and the aldehyde group, which afford intermediate **C**. In the fourth step, intramolecular Horner-Emmons type reaction does not occur under the condition, but the final product **3** is formed by elimination of one water molecule; the proposed reason is that the isolated product **3** is much more stable than the Horner-Emmons product **3'**, due to the presence of conjugation between the aromatic ring and the P=O system.

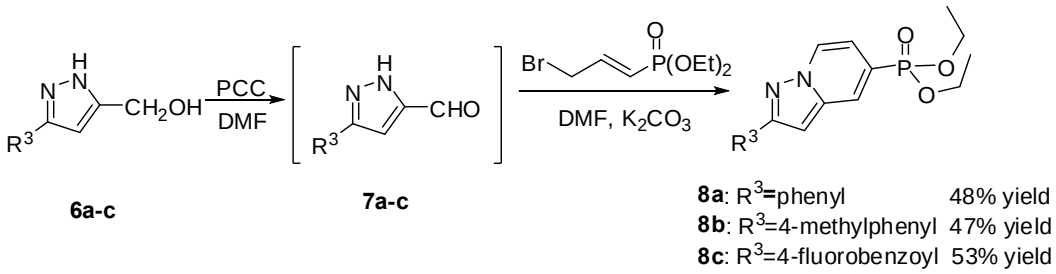


Scheme 1. Proposed mechanism for the one-pot tandem reaction

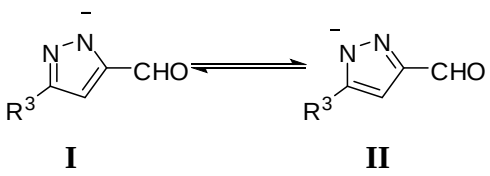
To examine the applicability of the tandem reaction in synthesizing other nitrogen bridgehead heterocycles bearing phosphonate moiety, we also used benzo[*d*]imidazole-2-carbaldehyde and pyrazole-5-carbaldehyde as substrates.



Scheme 2. Synthesis of pyrido[1,2-*a*]benzimidazole phosphonates **5**



Scheme 3. Synthesis of pyrazolo[1,5-*a*]pyridine phosphonate **8**

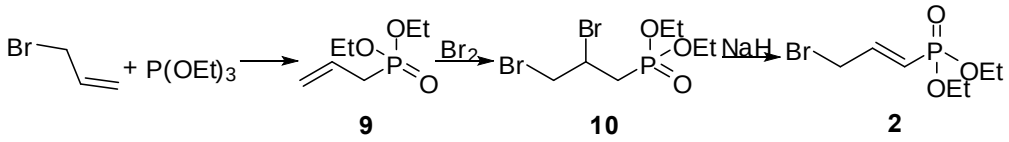


Scheme 4. Resonance structures of the deprotonated pyrazole carbaldehyde **7a-c**

As showed in Scheme 2, benzo[*d*]imidazole-2-carbaldehyde proceeded well under the same reaction conditions, and pyrido[1,2-*a*]benzimidazole phosphonates **5a, b** were obtained in moderate yields.

When 1*H*-pyrazole-5-carbaldehyde **7** was treated with diethyl 3-bromoprop-1-enylphosphonate **2** under the similar reaction conditions, a complex mixture was obtained. But raising the reaction temperature to 70 °C produced a moderate yield (Scheme 3). We assume that, the two resonance structures (Scheme 4) result in different reactivity from other two reactants of pyrrole-2-carbaldehyde and benzo[*d*]imidazole-2-carbaldehyde. At low temperature, it is kinetically-controlled procedure. The different position of electronegativity on the pyrazole carbaldehyde nitrogens gives different reaction points in the first step, intermolecular S_N2 reaction, in the proposed mechanism. This makes a complex mixcture resulted. At 70 °C, the reaction turns out to be thermodynamically controlled. Raising reaction temperature may be favourable for the effective intermediate **I**, which makes the reaction proceed as proposed reaction course.

In summary, we have demonstrated a novel tandem process which can be applied to the construction of nitrogen bridgehead heterocycles with phosphonates in moderate to good yields. Furthermore, the tandem reaction can be widely applied in synthesizing nitrogen bridgehead arylphosphonates including indolizine, pyrido[1,2-*a*]benzimidazole and pyrazolo[1,5-*a*]pyridine phosphonates. We believe that this method has great potential applications in nitrogen bridgehead arylphosphonates synthesis. Further efforts to investigate the reaction are ongoing in our group, and the results will be reported in the future.



Scheme 5. Synthesis of diethyl 3-bromoprop-1-enylphosphonate **2**

EXPERIMENTAL

All reagents were commercially available and used without further purification unless otherwise noted. Starting materials were prepared according to literatures. Melting points were recorded on an XD-4digital micro melting point apparatus and uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 300 MHz spectrometer, using $CDCl_3$ or DMSO-d_6 as solvent and TMS as internal standard. IR spectra were recorded with an IR spectrophotometer Avtar 370 FT-IR (Termo Nicolet). Elemental analyses were performed on a Vario EL III (Elementar Analysensysteme GmbH) spectroanalyzer. HRMS spectra were recorded on a Q-TOF6510 spectrograph (Agilent). Compounds **1a-g**,[31] **4a-b**,[32] **7a-c**[30a] were prepared according to the literatures.

General procedure for the synthesis of diethyl 3-bromoprop-1-enylphosphonate 2

Compound **2** was synthesized according to the literature method (Scheme 5).[33,34] To a 250-mL round-bottomed flask, triethyl phosphite (20 mL, 120 mmol) and allyl bromide (11 mL, 130 mmol) were added and the mixture was heated at 140 °C for 4 h. After evaporated under reduced pressure to remove the remaining ally bromide, the product, compound **9**, was purified by column chromatography. Dry CH_2Cl_2 was added to dissolve compound **9**, and the solution was cooled in an ice bath. Bromine (144 mmol) was added dropwise and the mixture was stirred for 2 h at rt. This mixture was poured into a saturated aqueous solution of Na_2SO_3, extracted with CH_2Cl_2 and dried over $MgSO_4$. After evaporation of the solvent, compound **10** was obtained as a pale yellow oil, which was subjected to the following steps without purification. NaH (40 mmol, 60%) was dispersed in 30 mL dry CH_2Cl_2 and the solution was cooled in an ice bath. Diethyl 2,3-dibromopropylphosphonate 10 (30 mmol) in 20 mL dry CH_2Cl_2 was added dropwise and the mixture was stirred for 24 h at rt. The temperature was raised to reflux for additional 1 h. After filtrated over celite and evaporation of the solvent, pale yellow oil **2** was purified by

column chromatography in 40% yield.

General procedure for the synthesis and analytical data of 3a-g

The mixture of compound **1** (1.5 mmol), compound **2** (1.8 mmol), potassium carbonate (3.3 mmol) and 40 mL DMF was stirred at 40 °C for 6-8 h. When TLC indicated the end of reaction, the reaction mixture was poured to water (50 mL), and extracted by EtOAc (15 mL×3). The combined extracts were washed by brine and dried over anhydrous $MgSO_4$. After concentrated under reduced pressure, the crude products were purified by column chromatography to afford **3a-g** in 65-84% yield.

Diethyl 2-propionylindolizin-7-ylphosphonate (3a)

pale yellow solid; mp 102-104 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.24 (t, *J* = 7.4 Hz, 3H), 1.34 (t, *J* = 7.1 Hz, 6H), 2.95 (q, *J* = 7.3 Hz, 2H), 4.04-4.24 (m, 4H), 6.74-6.80 (m, 1H), 7.03 (s, 1H), 7.88 (s, 1H), 7.91 (dd, *J* = 3.0 Hz, *J* = 7.2 Hz, 1H), 8.00 (d, *J* = 16.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 8.4, 16.3, 16.4, 33.3, 62.27, 62.34, 103.5, 112.1, 112.2, 116.3, 116.6, 118.9, 125.3, 125.5, 127.6, 127.8, 129.2, 131.2, 131.5, 197.6; IR (KBr) ν = 3133, 3063, 2983, 2938, 2905, 1668, 1628, 1470, 1387, 1287, 1249, 1198, 1020, 965, 789 cm^{-1}; ESI-MS *m/z* Calcd: 309.1. Found: 310.1 [M^++1]. *Anal.* Calcd for $C_{15}H_{20}NO_4P$: C, 58.25; H, 6.52; N, 4.53. Found: C, 58.27; H, 6.53; N, 4.55.

Diethyl 2-benzoylindolizin-7-ylphosphonate (3b)

brown solid; mp 103-105 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.35 (t, *J* = 7.1 Hz, 6H), 4.05-4.25 (m, 4H), 6.77-6.84 (m, 1H), 7.09 (s, 1H), 7.48-7.54 (m, 2H), 7.58-7.63 (m, 1H), 7.88-7.92 (m, 2H), 7.92-7.96 (m, 2H), 8.03 (d, *J* = 16.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 16.3, 16.4, 62.3, 62.4, 105.6, 112.2, 112.4, 116.6, 118.6, 119.2, 125.2, 125.4, 127.6, 127.8, 128.3, 128.4, 129.4, 131.1, 131.3, 132.2, 139.0, 191.4; IR (KBr) ν = 3138, 3060, 2981, 2941, 2900, 1641, 1470, 1318, 1240, 1024, 962, 795 cm^{-1}; ESI-MS *m/z* Calcd: 357.1. Found: 358.1 [M^++1]. *Anal.* Calcd for $C_{19}H_{20}NO_4P$: C, 63.86; H, 5.64; N, 3.92. Found: C, 63.87; H, 5.64; N, 3.90.

Diethyl 2-(4-methylbenzoyl)indolizin-7-ylphosphonate (3c)

pale yellow-green solid; mp 132-134 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.35 (t, *J* = 7.1 Hz, 6H), 2.46 (s, 3H), 4.05-4.25 (m, 4H), 6.77-6.82 (m, 1H), 7.07 (s, 1H), 7.31 (d, *J* = 7.8 Hz, 2H), 7.84 (d, *J* = 7.8 Hz, 2H), 7.87 (s, 1H), 7.92-7.95 (m, 1H), 8.03 (d, *J* = 16.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 16.3, 16.4, 21.6, 62.3, 62.4, 105.6, 112.1, 112.3, 116.4, 118.5, 119.0, 125.2, 125.4, 127.6, 127.8, 128.5, 129.1, 129.6, 131.0, 131.3, 136.3, 143.0, 191.1; IR(KBr) ν = 3136, 3059, 2980, 2900, 1630, 1470, 1320, 1244, 1026, 969, 782 cm^{-1}; ESI-MS *m/z* Calcd: 371.1. Found: 372.1 [M^++1]. *Anal.* Calcd for $C_{20}H_{22}NO_4P$: C, 64.68; H, 5.97; N, 3.77. Found: C, 64.66; H, 5.98; N, 3.77.

Diethyl 2-(4-methoxybenzoyl)indolizin-7-ylphosphonate (3d)

white solid; mp 167-169 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.35 (t, *J* = 7.1 Hz, 6H), 3.91 (s, 3H),

4.05-4.25 (m, 4H), 6.77-6.83 (m, 1H), 6.98-7.02 (m, 2H), 7.06 (s, 1H), 7.87 (s, 1H), 7.92-7.99 (m, 3H), 8.03 (d, J = 16.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 16.3, 16.4, 55.5, 62.26, 62.33, 105.5, 112.0, 112.2, 113.7, 118.2, 118.9, 125.2, 125.4, 127.6, 127.7, 128.6, 130.9, 131.2, 131.6, 131.8, 163.1, 190.1; IR(KBr) ν = 3129, 2980, 2937, 2905, 1629, 1600, 1572, 1469, 1316, 1242, 1168, 1017, 953, 769 cm^{-1}; ESI-MS *m/z* Calcd: 387.1. Found: 388.1 [M^++1]. *Anal.* Calcd for $C_{20}H_{22}NO_5P$: C, 62.01; H, 5.72; N, 3.62. Found: C, 62.03; H, 5.70; N, 3.59.

Diethyl 2-(4-chlorobenzoyl)indolizin-7-ylphosphonate (3e)

yellow-green solid; mp 136-138 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.35 (t, J = 7.1 Hz, 6H), 4.07-4.23 (m, 4H), 6.79-6.85 (m, 1H), 7.04 (s, 1H), 7.47-7.51 (m, 2H), 7.86-7.87 (m, 2H), 7.89-7.90 (m, 1H), 7.94 (dd, J = 7.1 Hz, J = 3.2 Hz, 1H), 8.03 (d, J = 16.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 16.3, 16.4, 62.3, 62.4, 105.5, 112.4, 112.5, 116.9, 118.4, 119.5, 125.2, 125.4, 127.6, 127.7, 127.9, 128.7, 128.9, 130.8, 130.9, 131.2, 131.4, 137.3, 138.7, 190.1; IR(KBr) ν = 3137, 2983, 2929, 1631, 1584, 1472, 1400, 1241, 1167, 1088, 1019, 954, 746 cm^{-1}; ESI-MS *m/z* Calcd: 391.1. Found: 392.1 [M^++1]. *Anal.* Calcd for $C_{19}H_{19}ClNO_4P$: C, 58.25; H, 4.89; N, 3.58. Found: C, 58.26; H, 4.90; N, 3.59.

Diethyl 2-(4-fluorobenzoyl)indolizin-7-ylphosphonate (3f)

yellowish brown solid; mp 123-124 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.36 (t, J = 7.1 Hz, 6H), 4.05-4.25 (m, 4H), 6.79-6.85 (m, 1H), 7.05 (s, 1H), 7.15-7.23 (m, 2H), 7.87 (s, 1H), 7.93-7.99 (m, 3H), 8.03 (d, J = 16.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 16.3, 16.4, 62.3, 62.4, 105.5, 112.3, 112.5, 115.4, 115.7, 118.4, 125.2, 125.4, 127.6, 127.7, 128.1, 131.1, 131.4, 131.9, 132.0, 135.17, 135.21, 163.6, 167.0, 189.9; IR(KBr) ν = 3136, 3064, 2983, 2939, 2901, 1640, 1594, 1504, 1470, 1387, 1318, 1240, 1155, 1082, 1024, 969, 886, 787 cm^{-1}; ESI-MS *m/z* Calcd: 375.1. Found: 376.1 [M^++1]. *Anal.* Calcd for $C_{19}H_{19}FNO_4P$: C, 60.80; H, 5.10; N, 3.73. Found: C, 60.81; H, 5.08; N, 3.73.

Diethyl 2-(4-nitrobenzoyl)indolizin-7-ylphosphonate (3g)

yellow solid; mp 168-170 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.36 (t, J = 7.1 Hz, 6H), 4.06-4.26 (m, 4H), 6.82-6.88 (m, 1H), 7.04 (s, 1H), 7.87 (s, 1H), 7.95 (dd, J = 7.2 Hz, J = 3.3 Hz, 1H), 8.01-8.07 (m, 3H), 8.36-8.38 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 16.3, 16.4, 62.36, 62.43, 105.3, 112.7, 112.9, 117.4, 118.7, 120.0, 123.6, 125.3, 125.5, 127.3, 127.6, 127.7, 130.1, 131.4, 131.6, 144.1, 149.8, 189.5; IR(KBr) ν = 3138, 2992, 1646, 1600, 1525, 1467, 1347, 1319, 1236, 1084, 1048, 1018, 961, 796 cm^{-1}; ESI-MS *m/z* Calcd: 402.1. Found: 403.1 [M^++1]. *Anal.* Calcd for $C_{19}H_{19}N_2O_6P$: C, 56.72; H, 4.76; N, 6.96. Found: C, 56.73; H, 4.77; N, 6.94.

General procedure for the synthesis and analytical data of 5a,b

Compounds **5a** and **5b** were obtained using the same method for **3a-g** in 57%, 63% yields, respectively.

3-Diethoxyphosphorylpyrido[1,2-*a*]benzimidazole (5a)

yellow-green solid; mp 114-116 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.38 (t, *J* = 7.1 Hz, 6H), 4.12-4.31 (m, 4H), 7.16-7.22 (m, 1H), 7.45-7.50 (m, 1H), 7.58-7.64 (m, 1H), 7.96 (d, *J* = 8.1Hz,1H), 8.03 (d, *J* = 8.1 Hz, 1H), 8.26 (d, *J* = 17.1 Hz, 1H), 8.54-8.58 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 16.3, 16.4, 62.86, 62.93, 110.8, 120.5, 122.6, 123.3, 123.5, 125.2, 125.4, 126.6, 128.5; IR(KBr) ν = 3032, 2979, 2924, 1502, 1484, 1467, 1391, 1320, 1244, 1089, 1031, 966, 792, 757 cm^{-1}; ESI-MS *m/z* Calcd: 304.1. Found: 305.1 [M^++1]. *Anal.* Calcd for $C_{15}H_{17}N_2O_3P$: C, 59.21; H, 5.63; N, 9.21. Found: C, 59.19; H, 5.64; N, 9.19.

3-Diethoxyphosphoryl-7,8-dimethylpyrido[1,2-*a*]benzimidazole (5b)

yellow-green solid; mp 146-147 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.37 (t, *J* = 7.2 Hz, 6H), 2.48 (s, 3H), 2.50 (s, 3H), 4.10-4.33 (m, 4H), 7.07-7.13 (m, 1H), 7.67 (s, 1H), 7.75 (s, 1H), 8.16 (d, *J* = 16.8 Hz, 1H), 8.43-8.47 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 16.3, 16.4, 20.7, 20.8, 62.7, 62.8, 109.8, 110.0, 110.5, 120.3, 123.4, 123.6, 125.0, 125.2, 127.2, 127.3, 129.9, 132.3, 136.1, 143.9, 146.1, 146.3; IR(KBr) ν = 3047, 2985, 2942, 1503, 1467, 1388, 1297, 1249, 1081, 1023, 963, 841, 778 cm^{-1}; ESI-MS *m/z* Calcd: 332.1. Found: 333.1 [M^++1]. *Anal.* Calcd for $C_{17}H_{21}N_2O_3P$: C, 61.44; H, 6.37; N, 8.43. Found: C, 61.43; H, 6.36; N, 8.44.

General procedure for the synthesis and analytical data of 8a-c

To a 50-mL round-bottomed flask were added **6a-c** (2.0 mmol), powdered pyridinium chlorochromate (0.86 g, 4 mmol) and DMF (10 mL). The mixture was stirred at rt for 3 h. Compound **2** (2.4 mmol) and potassium carbonate (4.4 mmol) were added when TLC indicated that compound **6a-c** was all oxidized to **7a-c**. The mixture was stirred at 70 °C for 8-12 h and then filtered. The filtrate was poured to water (50 mL) and extracted by EtOAc (15 mL×3). The combined extracts were washed by brine and then dried over anhydrous $MgSO_4$. After concentrated under reduced pressure, the crude products were purified by column chromatography to afford **8a-c** in 47-53% yield.

Diethyl 2-phenylpyrazolo[1,5-*a*]pyridin-5-ylphosphonate (8a)

white solid; mp 76-78 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.36 (t, *J* = 7.1 Hz, 6H), 4.10-4.25 (m, 4H), 6.96-7.02 (m, 2H), 7.36-7.42 (m, 1H), 7.44-7.50 (m, 2H), 7.95-8.00 (m, 2H), 8.09-8.15 (m, 1H), 8.50-8.54 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 16.3, 16.4, 62.5, 62.6, 96.2, 111.7, 111.8, 122.4, 124.0, 124.2, 125.0, 126.6, 128.4, 128.6, 128.8, 128.9, 132.6, 140.1, 140.4, 154.6; IR(KBr) ν = 3100, 3019, 2924, 2854, 1907, 1667, 1619, 1548, 1507, 1453, 1346, 1314, 1285, 1178, 1129, 1081, 997, 900, 784, 599 cm^{-1}; ESI-MS *m/z* Calcd: 330.1. Found: 331.1 [M^++1]. *Anal.* Calcd for $C_{17}H_{19}N_2O_3P$: C, 61.81; H, 5.80; N, 8.48. Found: C, 61.79; H, 5.81; N, 8.47.

Diethyl 2-*p*-tolylpyrazolo[1,5-*a*]pyridin-5-ylphosphonate (8b)

reddish oil, ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.36 (t, *J* = 7.1Hz, 6H), 2.40 (s, 3H), 4.09-4.25 (m, 4H), 6.93-7.00 (m, 2H), 7.27 (d, *J* = 7.8 Hz, 2H), 7.86 (d, *J* = 7.8 Hz, 2H), 8.10 (d, *J* = 16.2 Hz, 1H), 8.51 (dd,

J = 3.3 Hz, *J* = 6.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 16.3, 16.4, 21.3, 62.5, 62.6, 96.0, 111.5, 111.6, 122.2, 123.9, 124.1, 124.7, 126.5, 128.4, 128.6, 129.6, 129.8, 138.8, 140.1, 140.3, 154.7; IR(KBr) ν = 3110, 3028, 2976, 2924, 2858, 1924, 1725, 1620, 1546, 1518, 1462, 1338, 1284, 1244, 1091, 1019, 928, 784 cm^{-1}; ESI-MS *m/z* Calcd: 344.1. Found: 345.1 [M^++1]. *Anal.* Calcd for $C_{18}H_{21}N_2O_3P$: C, 62.78; H, 6.51; N, 8.14. Found: C, 62.80; H, 6.50; N, 8.14.

Diethyl 2-(4-fluorophenyl)pyrazolo[1,5-*a*]pyridin-5-ylphosphonate (8c)

white solid; mp 94-96 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.36 (t, *J* = 7.1 Hz, 6H), 4.07-4.25 (m, 4H), 6.91 (s, 1H), 6.96-7.02 (m, 1H), 7.12-7.18 (m, 2H), 7.92-7.97 (m, 2H), 8.11 (d, *J* = 16.2 Hz, 1H), 8.50 (dd, *J* = 3.0 Hz, *J* = 6.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 16.3, 16.4, 62.5, 62.6, 95.9, 111.7, 111.9, 115.7, 116.0, 122.7, 124.0, 124.1, 125.3, 128.3, 128.4, 128.6, 128.85, 128.90, 140.2, 140.4, 153.6, 161.6, 164.9; IR(KBr) ν = 3077, 2984, 2935, 2905, 1890, 1603, 1474, 1255, 1157, 1097, 1027, 969, 811, 769, 586 cm^{-1}; ESI-MS *m/z* Calcd: 348.1. Found: 349.1 [M^++1]. *Anal.* Calcd for $C_{17}H_{18}FN_2O_3P$: C, 58.62; H, 5.21; N, 8.04. Found: C, 58.63; H, 5.21; N, 8.05.

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