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Selective one-pot synthesis of substituted pyrrole-3-phosphonates from α-cyanomethyl-β-ketoesters

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Abstract—A one-step synthesis of 5-alkoxypyrrole-3-phosphonates is presented starting from suitable α-cyanomethyl-β-ketophosphonates. The key step in the synthesis involves a one-pot addition and heteroannulation sequence. The zinc perchlorate-catalyzed addition of alcohols to the nitrile carbon of α-cyanomethyl-β-ketophosphonates followed by annulation furnished 5-alkoxypyrrole-3-phosphonates. The addition–annulation process is carried out in the presence of water and 4,5-dihydro-5-oxo-1*H*-pyrrole-3-phosphonates (pyrrolinones) are obtained in good yields.
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1. Introduction

Pyrroles are an important class of heterocyclic compounds and are widely used in synthetic organic chemistry and material science.[1,2] Pyrroles are also often seen as building blocks in naturally occurring and biologically active compounds. Because of their multifunctional nature, these heterocycles can take part in several stereoselective transformations, such as conjugate additions,[3] cycloadditions,[4] acyliminium ion chemistry,[5] and allylic substitutions.[6]

Phosphonylated azaheterocycles are an important class of compounds with much biological potential as conformationally restricted bioisosteres of amino acids (Fig. 1).[7]

These compounds are useful as modulators for the excitability of the central nervous system as mediated by their ability to specifically act on the closed-channel binding sites of GABArho receptors.[8] Only a limited amount of research on the synthesis of these compounds has been conducted. Some examples are published for 2-phosphonopyrroles[9] but only a few examples have been reported for the synthesis of 3-phosphonopyrroles. The addition of enolates and enamines to phosphonoazoalkenes [10] or the addition of cyano methylphosphonate anion to azoalkenes was shown to lead to 3-phosphonopyrroles.[11]

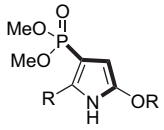

Figure 1.

The importance of these compounds has led us to apply our catalytic one-pot synthesis of substituted pyrrole carboxylate[12] to the synthesis of substituted pyrrole-3-phosphonates starting from α-cyanomethyl-β-ketophosphonates. Herein, we report the zinc perchlorate-catalyzed selective one-pot synthesis of substituted 5-alkoxypyrrole-3-phosphonates and pyrrolinone phosphonates from α-cyanomethyl-β-ketoesters and alcohols.

2. Results and discussion

α-Cyanomethyl-β-ketophosphonates **1a–c** were synthesized by the alkylation of commercially available β-ketophosphonate compounds with bromoacetonitrile (using either NaH/THF or DBU/benzene) in 72–78% yields according to the procedure from the literature.[12] In accordance with our previous work based on the $Zn(ClO_4)_2$ catalyzed heteroannulation reaction,[12] α-cyanomethyl-β-ketophosphonate **1a** and 5 mol % of $Zn(ClO_4)_2$ were heated to reflux in methanol with the reaction being monitored by TLC. Three different products were isolated after the work up and chromatographic separation. The isolated products were identified as a pyrrole derivative **3a** (as the major product), addition product **5a**, and pyrrolinone derivative **4a** (Scheme 1).

Keywords: Pyrroles; Heteroannulation; GABA analogs; β-Ketophosphonates; Pyrrolinones.
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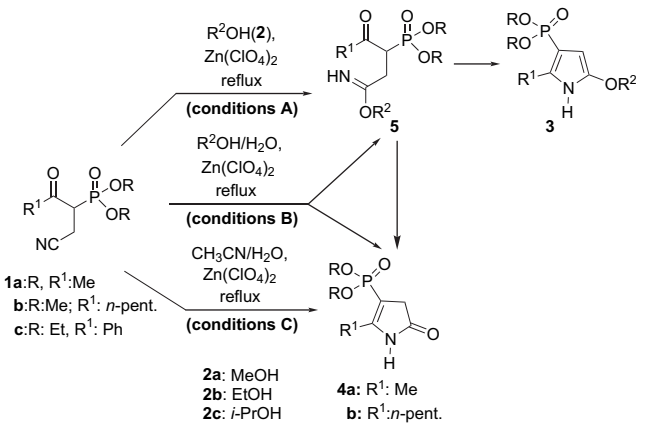


Scheme 1.

When this reaction was carried out in anhydrous methanol with 5 mol % of $Zn(ClO_4)_2$ the pyrrole derivative **3a** was isolated in 88% yield after chromatography (Scheme 1, conditions A). Using these conditions, various α-cyanomethyl-β-ketophosphonates derived from commercially available β-ketophosphonates and different alcohols are prepared as shown in Table 1. The 5-alkoxypyrrole-3-phosphonates were thus obtained in good to high yields.

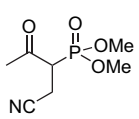
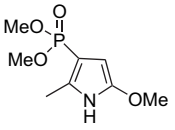
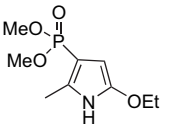
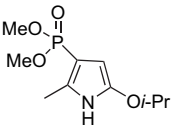
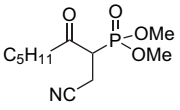
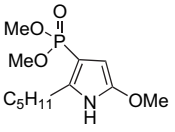
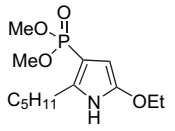
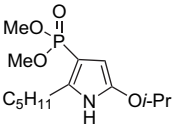
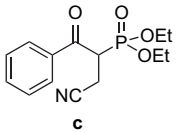
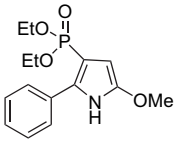
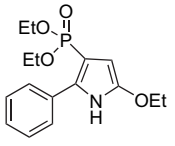
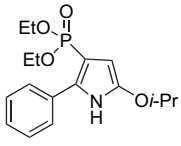
In an additional reaction, the addition–annulation reaction was carried out with **1b** in a MeOH/water (2:1) mixture at reflux in the presence of $Zn(ClO_4)_2$ (Scheme 1, conditions B). At the start of the reaction, only the formation of pyrrole **3d** was observed, in which the formation of pyrrolinone **4b** in an increasing amount along with the disappearance of pyrrole **3d** was subsequently observed. The only product isolated from the reaction was identified as pyrrolinone **4b** in 85% yield. The formation of pyrrolinone must proceed via the formation of pyrrole **3d** and then undergoes hydrolysis with water, as well as by the addition of water to the nitrile carbon followed by heteroannulation.

The typical pyrrole formation reaction with **1b** was carried out in a CH_3CN/water mixture (5:1) in the presence of $Zn(ClO_4)_2$ (conditions C). The TLC monitoring of these mixtures showed that **1b** was nearly completely converted into pyrrolinone **4b** (Scheme 1, conditions C). Under similar conditions, **1a** furnished **4a** in 87% yield.

The mechanism of pyrrole formation starting from α-cyanomethyl-β-ketoesters and anhydrous alcohols was investigated systematically. To demonstrate that an alcohol attack at the nitrile is the initial step, isolation of the corresponding iminoesters was carried out for **1a–c** as shown in Table 2. The reactions were stopped when an isolable amount of iminoesters was formed according to the TLC monitoring (3–4 h). After the work up and chromatographic separation, the corresponding iminoesters **5a–f** were isolated in 16–28% yields.

The present reaction can be rationalized by assuming that the anhydrous conditions and the attack of an external alcohol on the complex substrate form an iminoester complex. However, if the alcohol is used when wet, an attack of water on the formed iminoester and a direct attack on the complex afford a carboximide complex, which is the precursor of pyrolinone (Scheme 1).

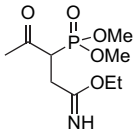
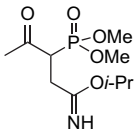
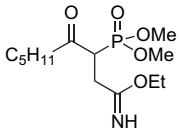
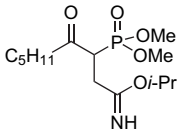
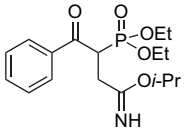
Table 1. Pyrroles synthesized by using condition A (Scheme 1)

Entry	α-Cyanomethyl-phosphonate **1**	Pyrrole **3**	Reaction time (h)	Yield (%)
1	 **a**	 **a**	6	88
2	**a**	 **b**	5	82
3	**a**	 **c**	6	72
4	 **b**	 **d**	7	80
5	**b**	 **e**	7	77
6	**b**	 **f**	6	83
7	 **c**	 **g**	8	87
8	**c**	 **h**	8	89
9	**c**	 **i**	7	79

3. Conclusions

Typically, when α-cyanomethyl-β-ketophosphonates were allowed to react with alcohols, as well as with water in the presence of $Zn(ClO_4)_2$, an addition to the nitrile triple bond of **1** and subsequent cyclocondensation occurred to

Table 2. Synthesized iminoesters

Entry	α-Cyanomethyl-phosphonate **1**	Iminophosphonate **5**	Reaction time (h)	Yield (%)
1	**a**	 **a**	3	22
2	**a**	 **b**	4	28
3	**b**	 **c**	2	25
4	**b**	 **d**	2	16
5	**c**	 **e**	3	20

afford 5-alkoxypyrroles and pyrolinones. Starting from α-cyanomethyl-β-ketophosphonates and alcohols in the presence of $Zn(ClO_4)_2$, the 5-alkoxypyrrole-3-phosphonates can be synthesized under water-free conditions in 72–89% yields. The same reaction was carried out in water–alcohol or in water, which furnished the pyrrolinones in 82–85% yields.

4. Experimental section

4.1. General

^1H and ^{13}C NMR spectra were obtained on a Bruker Avance 300 MHz, DPX 400 spectrometers. All of the resonances are referenced to the residual solvent signals. Elemental analyses: Leco CHNS 932 Analysator. IR spectra were obtained on Bruker IFS 66/s. Column chromatography was conducted on silica gel 60 (40–63 μm). TLC was carried out on aluminum sheets pre-coated with silica gel $60F_{254}$ (Merck), in which the spots were visualized with UV light (λ=254 nm). Commercially available $Zn(ClO_4)_2$ was used.

4.2. Dimethyl 1-cyano-3-oxobutan-2-ylphosphonate (1a)

Yield: 158 mg, 77%; yellow oil; R_f (MeOH/EtOAc 1:20) 0.50. IR (neat) ν_{max}: 3483, 3009, 2961, 2252, 1715, 1633, 1420 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 3.71–3.80 (6H, m, O*Me*), 3.44–3.55 (1H, m, C*H*CH_2), 2.54–2.75 (2H, m, CHC*H*$_2$CN), 2.36 (3H, s, *Me*). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 199.2, 117.3 (d, J=15.5 Hz), 53.4 (d, J=6.2 Hz), 53.3 (d, J=6.2 Hz), 48.4 (d, J=126.1 Hz), 30.4, 14.3. Anal. Calcd for $C_7H_{12}NO_4P$ (205.14): C, 40.98; H, 5.90; N, 6.83. Found: C, 40.71; H, 5.78; N, 6.69.

4.3. Dimethyl 1-cyano-3-oxooctan-2-ylphosphonate (1b)

Yield: 204 mg, 78%; yellow oil; R_f (MeOH/EtOAc 1:20) 0.55. IR (neat) ν_{max}: 3471, 3414, 2984, 2022, 1722, 1588 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 3.77–3.84 (6H, m, O*Me*), 3.47–3.59 (1H, m, C*H*CH_2), 2.85–3.05 (2H, m, CH_2), 2.54–2.78 (2H, m, CH_2), 1.58–1.69 (2H, m, CH_2), 1.22–1.39 (4H, m, CH_2CH_2), 0.89 (3H, t, J=6.6 Hz, CH_3CH$_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 202.0, 117.4 (d, J=16.9 Hz), 53.8 (d, J=6.3 Hz), 53.6 (d, J=6.5 Hz), 48.2 (d, J=126.6 Hz), 43.7, 31.0, 23.1, 22.3, 14.8, 14.6, 13.8. Anal. Calcd for $C_{11}H_{20}NO_4P$ (261.25): C, 50.57; H, 7.72; N, 5.36. Found: C, 50.63; H, 7.63; N, 5.28.

4.4. Diethyl 3-cyano-1-oxo-1-phenylpropan-2-yl-phosphonate (1c)

Yield: 215 mg, 73%; colorless oil; R_f (MeOH/EtOAc 1:20) 0.50. IR (neat) ν_{max}: 3420, 2291, 2253, 1595, 1448 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.39–7.95 (5H, m, *Ph*), 4.25–4.40 (1H, m, C*H*CH_2), 3.90–4.10 (4H, m, OCH_2CH$_3$), 3.0–3.10 (1H, m, CH_aH$_b$CH), 2.80–2.90 (1H, m, CH$_a$$H_b$CH), 1.21 (3H, t, J=7.0 Hz, OCH$_2$*Me*), 1.15 (3H, t, J=7.0 Hz, OCH$_2$*Me*). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 199.2, 136.2, 133.9, 129.1, 128.5, 117.4 (d, J=15.4 Hz), 63.3 (d, J=19.9 Hz), 60.0, 43.5 (d, J=126.0 Hz), 16.1 (d, J=6.1 Hz), 15.6 (d, J=6.0 Hz). Anal. Calcd for $C_{14}H_{18}NO_4P$ (295.27): C, 56.95; H, 6.14; N, 4.74. Found: C, 56.79; H, 6.04; N, 4.86.

4.5. General procedure for the synthesis of 5-alkoxypyrrole-3-phosphonates (3a–i)

α-Cyanomethyl-β-ketophosphonate (1 mmol) was dissolved in corresponding alcohol (10 mL) together with $Zn(ClO_4)_2$ (5 mol %). The reaction was refluxed for 5–8 h and monitored by TLC. The reaction mixture was extracted with ethyl acetate. The extract was dried over $MgSO_4$ and the solvent evaporated under reduced pressure, and the crude product was purified by column chromatography.

4.5.1. Dimethyl 5-methoxy-2-methyl-1*H*-pyrrol-3-yl-3-phosphonate (3a). Yield: 193 mg, 88%; yellow oil; R_f (MeOH/EtOAc 1:10) 0.60. IR (neat) ν_{max}: 3420, 3017, 2404, 1631, 1381 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 9.0 (1H, br s, N*H*), 5.31–5.36 (1H, m, C*H*), 3.74 (3H, s, O*Me*), 3.70 (6H, d, J=11.3 Hz, O*Me*), 2.36 (3H, s, *Me*). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 148 (d, J=19.6 Hz), 129.2 (d, J=22.7 Hz), 99.6 (d, J=202.8 Hz), 85.0 (d, J=13.7 Hz), 57.4, 52.0 (d, J=5.9 Hz), 12.3. Anal. Calcd for $C_8H_{14}NO_4P$ (219.17): C, 43.84; H, 6.44; N, 6.39. Found: C, 43.75; H, 6.35; N, 6.44.

4.5.2. Dimethyl 5-ethoxy-2-methyl-1*H*-pyrrol-3-yl-3-phosphonate (3b). Yield: 191 mg, 82%; colorless oil; R_f (MeOH/EtOAc 1:10) 0.64. IR (neat) ν_{max}: 3468, 3018,

2470, 1630, 1390 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.48 (1H, br s, N*H*), 5.21–5.28 (1H, m, C*H*), 3.96 (2H, q, J=7.0 Hz, OCH_2CH$_3$), 3.68 (6H, d, J=11.3 Hz, O*Me*), 2.34 (3H, s, *Me*), 1.33 (3H, t, J=7.0 Hz, OCH$_2$*Me*). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 146.7 (d, J=18.3 Hz), 129.0 (d, J=7.6 Hz), 99.4 (d, J=230.2 Hz), 85.8 (d, J=13.7 Hz), 66.0, 51.8 (d, J=4.5 Hz), 14.6, 12.2. Anal. Calcd for $C_9H_{16}NO_4P$ (233.2): C, 46.35; H, 6.92; N, 6.01. Found: C, 46.24; H, 6.79; N, 6.17.

4.5.3. Dimethyl 5-isopropoxy-2-methyl-1*H*-pyrrol-3-yl-3-phosphonate (3c). Yield: 178 mg, 72%; yellow oil; R_f (MeOH/EtOAc 1:10) 0.65. IR (neat) ν_{max}: 3416, 3016, 2461, 1631, 1381 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.25 (1H, br s, N*H*), 5.22–5.30 (1H, m, C*H*), 4.22–4.36 (1H, m, C*H*(CH$_3$)$_2$), 3.70 (6H, d, J=11.3 Hz, O*Me*), 2.36 (3H, s, *Me*), 1.30 (6H, d, J=6.1 Hz, CH(C*H*$_3$)$_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 145.3 (d, J=19.7 Hz), 128.7 (d, J=22.9 Hz), 99.8 (d, J=219.9 Hz), 87.2 (d, J=13.7 Hz), 73.6, 51.9 (d, J=5.0 Hz), 22.2, 12.4. Anal. Calcd for $C_{10}H_{18}NO_4P$ (247.22): C, 48.58; H, 7.34; N, 5.67. Found: C, 48.43; H, 7.41; N, 5.83.

4.5.4. Dimethyl 5-methoxy-2-pentyl-1*H*-pyrrol-3-yl-3-phosphonate (3d). Yield: 222 mg, 80%; yellow oil; R_f (MeOH/EtOAc 1:10) 0.68. IR (neat) ν_{max}: 3450, 3081, 2383, 1638, 1470 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.59 (1H, br s, N*H*), 5.31–5.37 (1H, m, C*H*), 3.78 (3H, s, O*Me*), 3.70 (6H, d, J=11.3 Hz, O*Me*), 2.76 (2H, t, J=7.4, C*H*$_2$), 1.54–1.62 (2H, m, C*H*$_2$), 1.29–1.33 (4H, m, C*H*$_2$), 0.87 (3H, t, J=6.6 Hz, C*H*$_3$CH$_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 147.8 (d, J=19.7 Hz), 134.0 (d, J=23.0 Hz), 99.7 (d, J=218.0 Hz), 85.0 (d, J=13.5 Hz), 57.4, 52.0 (d, J=6.0 Hz), 31.4, 29.9, 26.7, 22.5, 14.0. Anal. Calcd for $C_{12}H_{22}NO_4P$ (275.28): C, 52.36; H, 8.06; N, 5.09. Found: C, 52.19; H, 8.26; N, 5.27.

4.5.5. Dimethyl 5-ethoxy-2-pentyl-1*H*-pyrrol-3-yl-3-phosphonate (3e). Yield: 223 mg, 77%; colorless oil; R_f (MeOH/EtOAc 1:10) 0.70. IR (neat) ν_{max}: 3414, 3018, 2401, 1610, 1450 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.86 (1H, br s, N*H*), 5.58–5.61 (1H, m, C*H*), 3.98 (2H, q, J=7.0 Hz, OCH_2CH$_3$), 3.74 (6H, d, J=11.5 Hz, O*Me*), 2.64 (2H, t, J=7.5 Hz, C*H*$_2$), 1.49–1.58 (2H, m, C*H*$_2$), 1.22–1.35 (7H, m, C*H*$_3$C*H*$_2$C*H*$_2$), 0.87 (3H, t, J=7.0 Hz, C*H*$_3$CH$_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 146.6 (d, J=21.1 Hz), 132.9 (d, J=23.8 Hz), 98.6 (d, J=224.1 Hz), 86.8 (d, J=14.7 Hz), 66.5, 52.8 (d, J=4.8 Hz), 31.3, 29.5, 26.7, 22.4, 14.6, 13.9. Anal. Calcd for $C_{13}H_{24}NO_4P$ (289.31): C, 53.97; H, 8.36; N, 4.84. Found: C, 53.89; H, 8.16; N, 4.98.

4.5.6. Dimethyl 5-isopropoxy-2-pentyl-1*H*-pyrrol-3-yl-3-phosphonate (3f). Yield: 252 mg, 83%; colorless oil; R_f (MeOH/EtOAc 1:10) 0.68. IR (neat) ν_{max}: 3436, 3026, 2401, 1681, 1454 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.85 (1H, br s, N*H*), 5.21–5.29 (1H, m, C*H*), 4.05–4.20 (1H, m, OC*H*(CH$_3$)$_2$), 3.71 (6H, d, J=11.5 Hz, O*Me*), 2.78 (2H, t, J=7.6 Hz, C*H*$_2$), 1.55–1.65 (2H, m, C*H*$_2$), 1.25–1.40 (10H, m, C*H*$_2$C*H*$_2$, OCH(C*H*$_3$)$_2$), 0.87 (3H, t, J=6.6 Hz, C*H*$_3$CH$_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 145.4 (d, J=19.6 Hz), 133.3 (d, J=23.0 Hz), 99.9 (d, J=217.7 Hz), 87.4 (d, J=13.8 Hz), 74.0, 52.0 (d, J=4.8 Hz), 31.4, 29.8, 22.4, 21.9, 14.0, 13.8. Anal. Calcd for $C_{14}H_{26}NO_4P$ (303.3): C, 55.43; H, 8.64; N, 4.62. Found: C, 55.29; H, 8.71; N, 4.58.

4.5.7. Diethyl 5-methoxy-2-phenyl-1*H*-pyrrol-3-yl-3-phosphonate (3g). Yield: 268 mg, 87%; yellow oil; R_f (MeOH/EtOAc 1:10) 0.57. IR (neat) ν_{max}: 3479, 2950, 2253, 2020, 1631, 1474 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.32 (1H, br s, N*H*), 7.26–7.59 (5H, m, *Ph*), 5.68–5.72 (1H, m, C*H*), 3.94–4.05 (4H, m, OC*H*$_2$CH$_3$), 3.83 (3H, s, O*Me*), 1.16 (6H, t, J=7.0 Hz, OCH$_2$*Me*). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 148.9 (d, J=19.5 Hz), 131.8, 129.6, 129.0, 128.1, 127.7, 127.4, 104.8, 101.9, 89.1 (d, J=13.2 Hz), 61.4 (d, J=5.2 Hz), 57.4, 16.0 (d, J=6.1 Hz). Anal. Calcd for $C_{15}H_{20}NO_4P$ (309.29): C, 58.25; H, 6.52; N, 4.53. Found: C, 58.10; H, 6.39; N, 4.66.

4.5.8. Diethyl 5-ethoxy-2-phenyl-1*H*-pyrrol-3-yl-3-phosphonate (3h). Yield: 289 mg, 89%; yellow oil; R_f (MeOH/EtOAc 1:10) 0.60. IR (neat) ν_{max}: 3413, 2971, 2021, 1635, 1475 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.53 (1H, br s, N*H*), 7.28–7.61 (5H, m, *Ph*), 5.66–5.71 (1H, m, C*H*), 3.90–4.14 (6H, m, OC*H*$_2$Me), 1.38 (3H, t, J=7.0 Hz, OCH$_2$*Me*), 1.14 (6H, t, J=7.0 Hz, OCH$_2$*Me*). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 147.7 (d, J=9.6 Hz), 131.9, 129.5, 129.2, 128.1, 127.7, 127.2, 104.6, 101.7, 89.9 (d, J=13.2 Hz), 66.2, 61.4 (d, J=5.2 Hz), 16.1 (d, J=7.0 Hz), 14.1. Anal. Calcd for $C_{16}H_{22}NO_4P$ (323.32): C, 59.44; H, 6.86; N, 4.33. Found: C, 59.31; H, 6.72; N, 4.41.

4.5.9. Diethyl 5-isopropoxy-2-phenyl-1*H*-pyrrol-3-yl-3-phosphonate (3i). Yield: 265 mg, 79%; yellow oil; R_f (MeOH/EtOAc 1:10) 0.62. IR (neat) ν_{max}: 3514, 2954, 2022, 1633, 1475 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.21 (1H, br s, N*H*), 7.27–7.61 (5H, m, *Ph*), 5.68–5.72 (1H, m, C*H*), 4.35–4.43 (1H, m, C*H*(CH$_3$)$_2$), 3.90–4.10 (4H, m, OC*H*$_2$Me), 1.35 (6H, d, J=6.1 Hz, CH(C*H*$_3$)$_2$), 1.17 (6H, t, J=7.0 Hz, OCH$_2$*Me*). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 146.8 (d, J=19.5 Hz), 131.9, 129.2, 128.9, 128.2, 127.6, 127.3, 105.0, 102.1, 88.3 (d, J=13.1 Hz), 73.9, 61.4 (d, J=5.2 Hz), 29.7, 16.1 (d, J=7.0 Hz). Anal. Calcd for $C_{17}H_{24}NO_4P$ (337.35): C, 60.53; H, 7.17; N, 4.15. Found: C, 60.57; H, 7.38; N, 4.33.

4.5.10. Dimethyl 4,5-dihydro-2-methyl-5-oxo-1*H*-pyrrol-3-yl-3-phosphonate (4a). Yield: 111 mg, 54%; yellow oil; R_f (MeOH/EtOAc 1:10) 0.30. IR (neat) ν_{max}: 3440, 2988, 2933, 2445, 1728, 1598, 1455 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.05 (1H, br s, N*H*), 3.67 (6H, d, J=11.2 Hz, O*Me*), 3.09 (2H, s, C*H*$_2$), 2.22 (3H, s, C*H*$_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.2, 153.5, 95.0 (d, J=224.2 Hz), 51.1 (d, J=4.7 Hz), 37.9 (d, J=9.2 Hz), 12.4. Anal. Calcd for $C_7H_{12}NO_4P$ (205.14): C, 40.98; H, 5.90; N, 6.83. Found: C, 40.71; H, 5.88; N, 6.54.

4.5.11. Dimethyl 4,5-dihydro-5-oxo-2-pentyl-1*H*-pyrrol-3-yl-3-phosphonate (4b). Yield: 191 mg, 73%; colorless oil; R_f (MeOH/EtOAc 1:20) 0.45. IR (neat) ν_{max}: 3450, 2481, 2928, 2462, 1725, 1596, 1449, 1248 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.15 (1H, br s, N*H*), 3.74 (6H, d, J=11.2 Hz, O*Me*), 3.19 (2H, s, C*H*$_2$), 2.74 (2H, t, J=7.2 Hz, CH$_2$C*H*$_2$), 1.56–1.63 (2H, m, CH$_3$C*H*$_2$CH$_2$), 1.35–1.37 (4H, m, CH$_2$C*H*$_2$C*H*$_2$), 0.91 (3H, t, J=6.9 Hz,

CH_3CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 179.6, 158.5, 96.2 (d, J=224.7 Hz), 52.1 (d, J=4.8 Hz), 38.9 (d, J=9.7 Hz), 31.2, 27.3, 27.2, 22.3, 13.8. Anal. Calcd for $C_{11}H_{20}NO_4P$ (261.3): C, 50.57; H, 7.72; N, 5.36. Found: C, 50.69; H, 7.64; N, 5.24.

4.5.12. Dimethyl 5-ethoxy-5-imino-2-oxopentane-3-ylphosphonate (5a). Yield: 56 mg, 22%; colorless oil; R_f (MeOH/EtOAc 1:10) 0.68. IR (neat) ν_{max}: 3481, 3417, 3005, 1724 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 4.10 (2H, q, J=7.0 Hz, OCH_2Me), 3.76 (6H, d, J=11.1 Hz, O*Me*), 3.63–3.72 (1H, m, $CHCH_2$), 3.06–3.15 (1H, m, CH_aH_bCH), 2.61–2.69 (1H, m, CH_aH_bCH), 2.41 (3H, s, *Me*), 1.25 (3H, t, J=7.0 Hz, OCH_2Me). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 201.6 (d, J=4.2 Hz), 171.0 (d, J=19.2 Hz), 61.0, 53.8 (d, J=6.6 Hz), 53.4 (d, J=6.6 Hz), 48.2 (d, J=127.2 Hz), 31.6, 31.3 (d, J=2.9 Hz), 14.1. Anal. Calcd for $C_9H_{18}NO_5P$ (251.21): C, 43.03; H, 7.22; N, 5.58. Found: C, 43.06; H, 7.23; N, 5.64.

4.5.13. Dimethyl 5-isopropoxy-5-imino-2-oxopentane-3-ylphosphonate (5b). Yield: 73 mg, 28%; colorless oil; R_f (MeOH/EtOAc 1:10) 0.70. IR (neat) ν_{max}: 3495, 3051, 2754, 1724, 1391 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 4.91–5.0 (1H, m, $CH(CH_3)_2$), 3.76 (6H, d, J=11.0 Hz, O*Me*), 3.68–3.74 (1H, m, CH_aH_bCH), 3.06–3.15 (1H, m, CH_aH_bCH), 2.58–2.71 (1H, m, CH_aH_bCH), 2.42 (3H, s, *Me*), 1.22 (3H, d, J=6.1 Hz, CH_3CH), 1.21 (3H, d, J=6.1 Hz, CH_3CH). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 201.7, 170.5 (d, J=19.5 Hz), 68.6, 53.7 (d, J=6.6 Hz), 53.4 (d, J=6.6 Hz), 48.7 (d, J=127.2 Hz), 31.6 (d, J=3.4 Hz), 31.4, 21.7 (d, J=2.6 Hz). Anal. Calcd for $C_{10}H_{20}NO_5P$ (265.24): C, 45.28; H, 7.60; N, 5.28. Found: C, 45.29; H, 7.49; N, 5.37.

4.5.14. Dimethyl 1-ethoxy-1-imino-4-oxononan-3-ylphosphonate (5c). Yield: 75 mg, 25%; colorless oil; R_f (MeOH/EtOAc 1:10) 0.75. IR (neat) ν_{max}: 3352, 3063, 2991, 2479, 1718, 1595 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 4.08–4.14 (2H, q, J=7.1 Hz, OCH_2CH_3), 3.76 (6H, d, J=11.1 Hz, O*Me*), 3.62–3.75 (1H, m, $CHCH_2$), 3.10–3.20 (1H, m, CH_aH_bCH), 2.80–2.87 (1H, m, CH_aH_bCH), 2.60–2.73 (2H, m, CH_2), 1.58–1.70 (2H, m, CH_2), 1.25–1.38 (4H, m, CH_2), 1.23 (3H, t, J=7.1 Hz, OCH_2CH_3), 0.89 (3H, t, J=7.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 204.4 (d, J=4.2 Hz), 171.2 (d, J=19.5 Hz), 61.1, 53.5 (d, J=6.6 Hz), 53.1 (d, J=6.6 Hz), 47.6 (d, J=127.3 Hz), 44.0, 31.1 (J=2.9 Hz), 31.0, 23.0, 22.4, 14.1, 13.9. Anal. Calcd for $C_{13}H_{26}NO_5P$ (307.32): C, 50.81; H, 8.53; N, 4.56. Found: C, 50.73; H, 8.39; N, 4.49.

4.5.15. Dimethyl 1-isopropoxy-1-imino-4-oxononan-3-ylphosphonate (5d). Yield: 52 mg, 16%; colorless oil; R_f (MeOH/EtOAc 1:10) 0.70. IR (neat) ν_{max}: 3450, 3005, 2027, 1724 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 4.9–5.0 (1H, m, $OCH(CH_3)_2$), 3.77 (3H, d, J=11.0 Hz, O*Me*), 3.76 (3H, d, J=11.0 Hz, O*Me*), 3.62–3.75 (1H, m, $CHCH_2$), 3.08–3.18 (1H, m, CH_aH_bCH), 2.80–2.85 (1H, m, CH_aH_bCH), 2.60–2.65 (2H, m, CH_2), 1.60–1.65 (2H, m, CH_2), 1.24–1.38 (4H, m, CH_2), 1.21–1.23 (6H, m, $CH(CH_3)_2$), 0.87 (3H, t, J=7.0 Hz, CH_3CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 204.4 (d, J=4.2 Hz), 170.8 (d, J=19.5 Hz), 68.7, 53.4 (d, J=6.6 Hz), 53.0 (d, J=6.6 Hz), 47.3 (d, J=127.0 Hz), 44.1, 31.4 (d, J=2.8 Hz), 31.0, 23.0, 22.4, 21.7 (d, J=2.2 Hz), 13.9. Anal. Calcd for $C_{14}H_{28}NO_5P$ (321.35): C, 52.33; H, 8.78; N, 4.36. Found: C, 52.09; H, 8.59; N, 4.47.

4.5.16. Diethyl 4-isopropoxy-4-imino-1-oxo-1-phenylbutane-2-ylphosphonate (5e). Yield: 72 mg, 20%; colorless oil; R_f (MeOH/EtOAc 1:10) 0.65. IR (neat) ν_{max}: 3470, 2981, 2032, 1727, 1469 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 8.04 (2H, d, J=7.5 Hz), 7.45–7.60 (3H, m, *Ph*), 4.87–4.96 (1H, m, $CH(CH_3)_2$), 4.54–4.64 (1H, m, $CHCH_2$), 3.95–4.15 (4H, m, OCH_2Me), 3.33–3.42 (1H, m, CH_aH_bCH), 2.87–2.94 (1H, m, CH_aH_bCH), 1.26 (3H, t, J=7.0 Hz, OCH_2Me), 1.12–1.16 (9H, m, OCH_2Me and $CH(CH_3)_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 195.2, 170.6, 137.4, 133.2, 128.9, 128.4, 68.7, 62.9 (d, J=3.2 Hz), 43.3 (d, J=127.8 Hz), 32.5, 21.7 (d, J=8.3 Hz), 16.1 (d, J=12.4 Hz), 16.0. Anal. Calcd for $C_{17}H_{26}NO_5P$ (355.37): C, 57.46; H, 7.37; N, 3.94. Found: C, 57.31; H, 7.49; N, 3.87.

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