



Highly selective intermolecular one-pot three component 1,3-dipolar cycloaddition reaction of aldehydes, with phosphonates and proline



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ABSTRACT

The use of L-proline to act as an organocatalyst in the aldol reaction of acylphosphonates and non enolizable aldehydes failed; however, it reacted with the aldehydes to afford azomethine ylides after decarboxylation that in turn underwent 1,3-dipolar cycloaddition with the acylphosphonates to form a bicyclic hexahydropyrrolo[1,2-c]oxazol-1-ylphosphonates in good yield. No azomethine ylide formation was observed on the reaction of acylphosphonates with proline.

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1. Introduction

The proline catalyzed enantioselective intramolecular aldol reaction was developed in the 1970s and later on List et al.¹ developed the first intermolecular aldol reactions between aldehydes and ketones with high stereoselectivities. The reported results from List offered simple solutions to one of the most important problems in catalytic asymmetric synthesis and presented a new use of small organic molecules as catalysts in organic chemistry.²

The development of (L)-proline as an organocatalyst, which is known as the simplest enzyme, is an important cornerstone in the area of organocatalysis because it can be applied as a catalyst in a wide range of asymmetric reactions with excellent stereoselectivities, and in particular it provides high efficiency in the enantioselective direct aldol reaction. Proline is one of the most prominent catalysts in a wide range of asymmetric reactions.²

We are currently interested in acylphosphonates, which led us to develop several methodologies.³ In connection with the previous work, we intended to use acylphosphonates in proline catalyzed aldol reactions. As far as we know, no such work has been published before. The aldol products between phosphonate and non

enolizable aldehyde could give interesting structures for further functionalization to obtain drug intermediates.

2. Results and discussion

As an initial reaction, acylphosphonate **4** was reacted with benzaldehyde (**1**) in the presence of 20% mol of L-proline (**2**) in DMSO and monitored by TLC. After 5 h, a new spot on TLC was observed and was isolated. The both ¹H and ¹³C NMR spectrum of the product indicated that the reaction had not proceeded to form the desired aldol product but rather some cyclization products in very low yield. Then, the reactions were carried out using different solvents at various temperatures. DMSO, dichloromethane, THF, chloroform, DMF, dimethoxyethane, and water were used as the solvent, but none of them worked as well as DMSO by TLC analysis. Therefore, the reactions were performed in DMSO at different temperatures. At a low temperature, (<5 °C) no product formation was observed (80% DMSO, 20% THF). At high temperatures, (>100 °C) acylphosphonates were decomposed.

The reaction scope was studied by using a variety of catalysts and additives. As we reported earlier, L-proline was used with thiourea.⁴ Its functionality was responsible for catalytic activity and the fact that the carbonyl group of the aldehyde interacts with the catalyst via a dual H-bond interaction to the urea protons. However, none of these catalysts worked as well as L-proline. Perhaps thiourea blocks the decarboxylation of proline (Fig. 1). The cyclic

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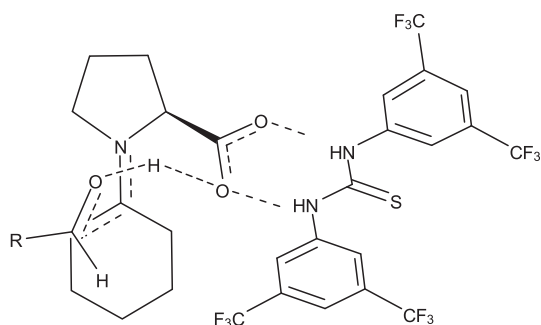


Fig. 1. General reaction scheme of 1,3 dipolar cycloaddition.

product that was obtained in all the reactions in low yield was identified as pyrrolo-oxazolyl phosphonate, which could have the following possible structures (5–6) as shown in Scheme 1.

L-Proline failed to act as an organocatalyst in the aldol reaction of acylphosphonates with non-enolizable aldehydes; however, proline reacted with the aldehydes to give azomethine ylides after decarboxylation that in turn underwent 1,3-dipolar cycloaddition with the acylphosphonates.

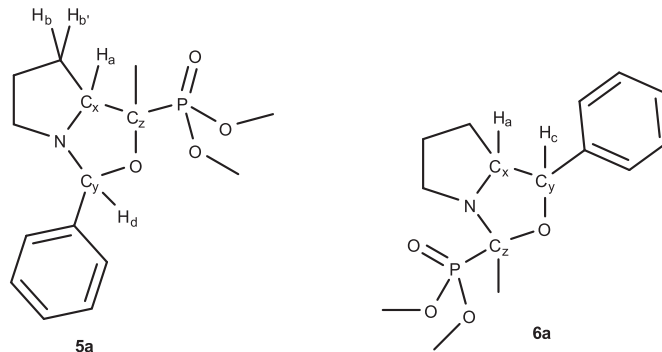
1,3-Dipolar cycloaddition is a classic reaction in organic chemistry, which is also known as the Huisgen cycloaddition, the reaction of a dipolarophile with a 1,3-dipolar compound that provides five-membered heterocycles. 1,3-Dipolar cycloadditions are very important transformations in organic chemistry, as can be seen by the large number of targets that can be prepared using this chemistry. After its discovery, this reaction has developed into a generally useful method for the formation of five-membered heterocycles, which can be applied using a wide selection of 1,3-dipoles and dipolarophiles and controllable regio- and stereo-selectivity during the cycloaddition. The method allows for further transformations of the cycloadducts into a variety of molecules with various functionalities. Several natural and unnatural products have been prepared by syntheses that have a 1,3-dipolar cycloaddition as a crucial step.⁵ In the literature formation of azomethine ylides after decarboxylation is reported.⁶

Close inspection of the NMR data indicated that only structure 5 could be the products as described in the mechanism below.

The reaction of benzaldehyde with proline gives iminium salt **3a**, which then undergoes a decarboxylation reaction to form an azomethine ylide **3b**. The 1,3-dipolar cycloaddition of this azomethine ylide with the carbonyl group of acylphosphonate **4a** then furnished the product **5a** (Scheme 2). Decarboxylation followed by 1,3-dipolar cycloaddition was reported by Dondoni et al. using ethyl pyruvate and proline. In this two component reaction L-proline failed to act as an organocatalyst in the homoaldol reaction of ethyl pyruvate. However, it gives an azomethine ylide that in turn underwent reaction with a second molecule of pyruvate under L-proline catalysis to form isotetronic acid.⁷

It is also possible that the first iminium ion is formed with acylphosphonate and then decarboxylation furnishes azomethine ylide **3e**, which gives a 1,3-dipolar cycloaddition reaction to form the product **6a** (Scheme 3).

Inspection of both structures by ¹H NMR, ¹³C NMR, and COSY experiments show that the structure is **5a**. In the ¹H NMR spectrum, all the peaks are in agreement with the structure **5a**.



In ¹H NMR and COSY experiments, the proton *d* has no interaction with the proline ring protons *b* and *b'*, and no interaction of proton *a* with proton *c* is observed. Proton *d* has a long-range coupling with the aromatic protons. In the ¹H NMR spectrum, the proton *a* exhibits a double doublet signal at 5.12 ppm and proton *d* a doublet signal at 5.26 ppm.¹³C NMR techniques demonstrate two CH and one quaternary C signals besides the aromatic carbon peaks, from C_x, C_y, and C_z. Two CH carbons give a doublet at 97.2 ppm and 82.6 ppm because of C-P coupling. One quaternary carbon gives a singlet at 67.5 ppm.

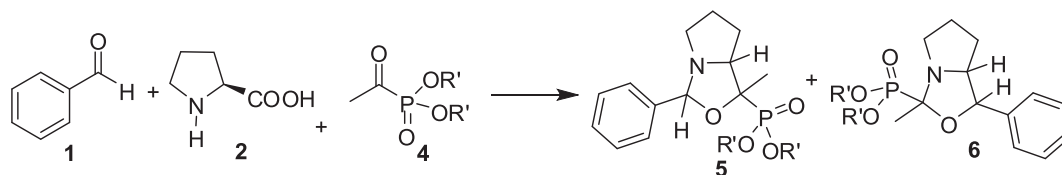
After the determination of the structure, optimization of the reaction was undertaken in which mainly the equivalencies of the reaction partners were changed under optimized conditions 1 mmol arylaldehyde **1** was dissolved in DMSO, and then 2 equiv. of dimethyl alkylphosphonate **4** in DMSO and 1.1 equiv. of L-proline **2** were added. After purification, the product was isolated in 65% yield. Using these conditions, several products were synthesized as shown in Table 1.

As shown in Table 1, proline and thioproline were used as amino acids and reacted with various aromatic aldehydes to form azomethine ylides, which underwent 1,3-dipolar cycloaddition with the carbonyl group of the acylphosphonates to form the products. Additional experiments were carried out to form azomethine ylide using acylphosphonate but they failed. This showed that azomethine formation was not possible using only phosphonates to obtain bis phosphonate derivatives.

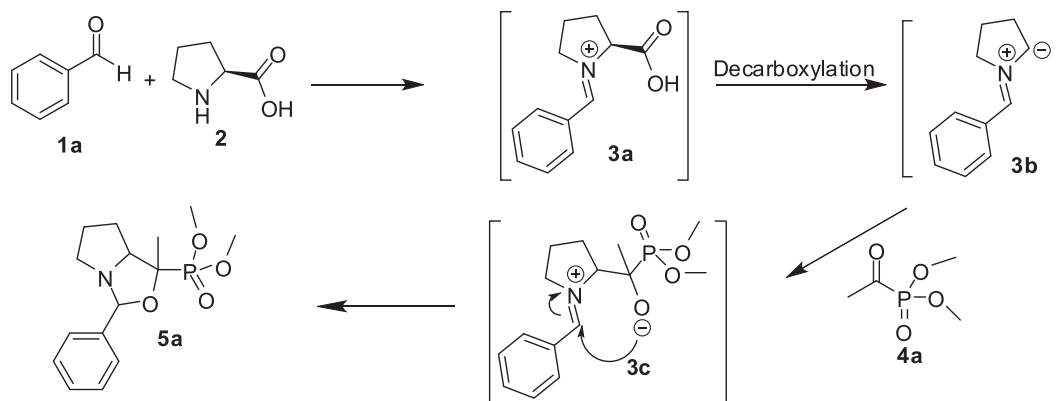
One of the drawbacks of this methodology is that only aliphatic phosphonates give a reaction and tert-butylphosphonates give no reaction due to the steric hindrance. The advantage of the reaction is high selectivity.

3. Conclusion

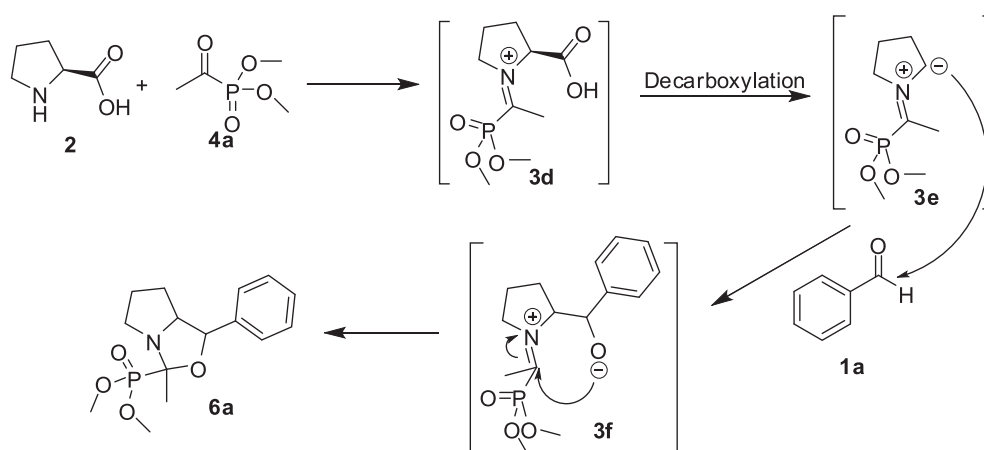
We developed a highly selective intermolecular one-pot three component 1,3-dipolar cycloaddition reaction with aromatic aldehydes, acylphosphonates, and proline to synthesize bicyclic hexahydroindolizino[1,2-c]oxazol-1-yl phosphonates in good yield. The acylphosphonates give on reaction with proline, no azomethine



Scheme 1.



Scheme 2.



Scheme 3.

ylides. This parasitic reaction of proline in organocatalytic reactions can be used to synthesize interesting heterocycles.

4. Experimental section

4.1. General

^1H and ^{13}C NMR spectra were obtained on Bruker Avance DPX 400 spectrometers at 400 MHz for ^1H and 100 MHz for ^{13}C . All of the resonances are referenced to the residual solvent signals (CDCl_3 for ^1H NMR; CDCl_3 for ^{13}C NMR). Elemental analyses: Leco CHNS 932 Analyzer (Central laboratory from Hacettepe University and METU). The IR spectra were obtained on a Bruker IFS 66/s. Column chromatography was conducted on silica gel 60 (40–63 μm). TLC was carried out on aluminum sheets that were pre-coated with silica gel 60F254 (Merck), in which the spots were visualized with UV light (λ 254 nm).

4.2. General procedure for the 1,3-dipolar cycloaddition reactions

1 mmol of arylaldehyde was dissolved in DMSO (1 mL). Then, 2 mmol of dimethyl acylphosphonate, which was dissolved in DMSO (1 mL), and separately 1.1 mmol of proline was added slowly to the stirred solution of arylaldehyde at rt under an argon atmosphere. The reaction mixture was stirred for 1–2 days and monitored by TLC. The reaction was diluted with ethyl acetate (15 mL) and brine (15 mL). The aqueous phase was extracted with ethyl acetate (3 \times 30 mL). The combined organic layers were dried over

MgSO_4 and concentrated under reduced pressure. The crude mixture was purified on silica gel with EtOAc as eluent.

4.2.1. Dimethyl 1-methyl-3-phenylhexahydropyrrolo[1,2-c]oxazol-1-ylphosphonate **5a**

Colourless oil, (209 mg, 65%). ^1H NMR (400 MHz, CDCl_3) δ 0.85 (d, $J = 15.5$ Hz, 3H), 1.74–1.83 (m, 1H), 1.85–2.01 (m, 2H), 2.08–2.17 (m, 1H), 2.72–2.78 (m, 1H), 2.87–2.94 (m, 1H), 3.75–3.83 (m, 6H), 5.1 (dd, $J_1 = 1.7$ Hz, $J_2 = 5.5$ Hz, 1 H), 5.22 (d, $J = 13.6$ Hz, 1 H), 7.13–7.27 (m, 5H); ^{13}C NMR (100 MHz, CDCl_3) δ 14.7, 24.2, 28.7, 46.0 (d, $J_{\text{C-P}} = 11.1$ Hz), 52.3 (d, $J_{\text{C-P}} = 16.9$ Hz), 53.2 (d, $J_{\text{C-P}} = 7.3$ Hz), 66.3, 82.1 (d, $J_{\text{C-P}} = 10.7$ Hz), 95.9 (d, $J_{\text{C-P}} = 6.5$ Hz), 125.6, 126.5, 127.0, 137.2; IR (cm^{-1}) 3331, 2973, 2882, 1379. Anal. Calcd. for $\text{C}_{15}\text{H}_{22}\text{NO}_4\text{P}$ (311.13): C, 57.87; H, 7.12; N, 4.50 Found: C, 57.56; H, 7.38; N, 4.29.

4.2.2. Dimethyl 1-methyl-3-(4-nitrophenyl)hexahydropyrrolo[1,2-c]oxazol-1-ylphosphonate **5b**

Colourless oil, (177 mg, 63%). ^1H NMR (400 MHz, CDCl_3) δ 0.85 (d, $J = 17.3$ Hz, 3H), 1.76–1.85 (m, 1H), 1.86–2.04 (m, 2H), 2.11–2.20 (m, 1H), 2.74–2.79 (m, 1H), 2.82–2.89 (m, 1H), 3.76–3.84 (m, 6H), 5.12 (dd, $J_1 = 1.0$ Hz, $J_2 = 5.2$ Hz, 1 H), 5.26 (d, $J = 13.6$ Hz, 1 H), 7.78 (dd, $J_1 = 8.6$ Hz, $J_2 = 10.3$ Hz, 4 H); ^{13}C NMR (100 MHz, CDCl_3) δ 16.0, 25.1, 29.7, 47.3 (d, $J_{\text{C-P}} = 10.8$ Hz), 53.2 (d, $J_{\text{C-P}} = 7.6$ Hz), 54.1 (d, $J_{\text{C-P}} = 8.1$ Hz), 67.5, 82.6 (d, $J_{\text{C-P}} = 1.3$ Hz), 97.2 (d, $J_{\text{C-P}} = 6.2$ Hz), 123.1, 127.3, 146.3 (d, $J_{\text{C-P}} = 5.0$ Hz), 147.7; IR (cm^{-1}) 3566, 3332, 2973, 2881, 1456. Anal. Calcd. for $\text{C}_{15}\text{H}_{21}\text{N}_2\text{O}_6\text{P}$ (356.11): C, 50.56; H, 5.94; N, 7.86 Found: C, 50.24; H, 5.78; N, 7.61.

Table 1
Synthesis of 1,3-dipolar cycloaddition-products **5a-k**.

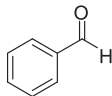
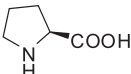
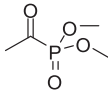
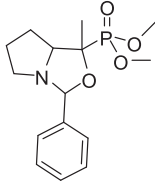
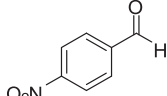
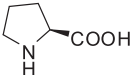
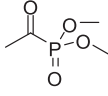
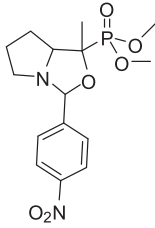
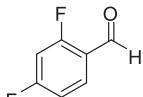
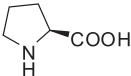
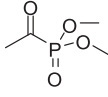
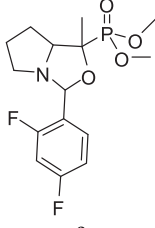
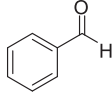
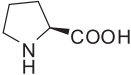
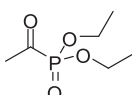
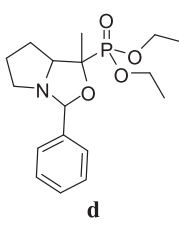
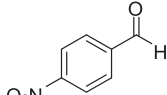
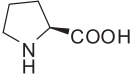
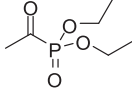
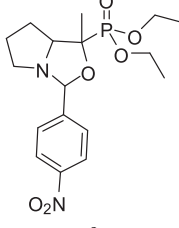
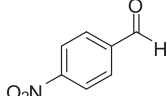
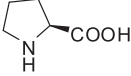
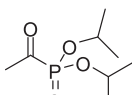
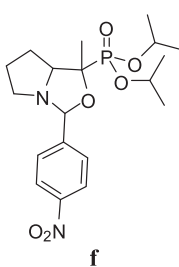
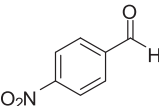
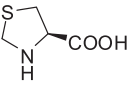
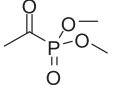
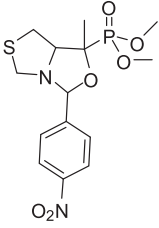
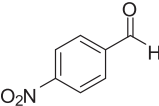
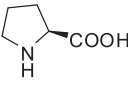
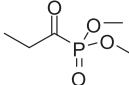
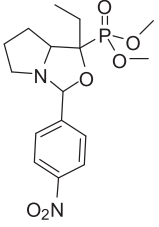
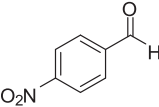
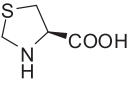
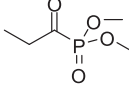
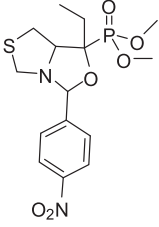
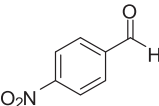
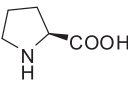
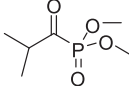
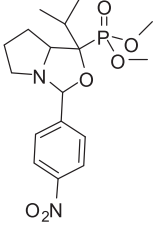
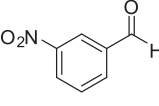
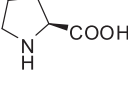
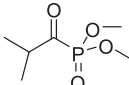
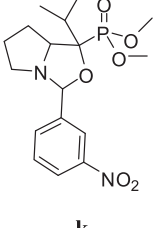
Entry	Aldehyde 1	Proline Derivative 2	Phosphonate 4	Product 5	Yield (%)
1	 a	 a	 a	 a	65
2	 b	 a	 a	 b	63
3	 c	 a	 a	 c	61
4	 a	 a	 b	 d	59
5	 b	 a	 b	 e	65
6	 b	 a	 c	 f	64

Table 1 (continued)

Entry	Aldehyde 1	Proline Derivative 2	Phosphonate 4	Product 5	Yield (%)
7					63
8					63
9					61
10					62
11					63

4.2.3. Dimethyl 3-(2,4-difluorophenyl)-1-methylhexahydropyrrolo[1,2-c]oxazol-1-ylphosphonate **5c**

Yellow oil, (176 mg, 61%). ¹H NMR (400 MHz, CDCl₃) δ 0.88 (d, *J* = 15.8 Hz, 3H), 1.76–1.85 (m, 1H), 1.88–2.02 (m, 2H), 2.09–2.21 (m, 1H), 2.75–2.83 (m, 1H), 2.86–2.93 (m, 1H), 3.73–3.84 (m, 6H), 5.26 (d, *J* = 5.1 Hz, 1H), 5.46 (d, *J* = 13.8 Hz, 1H), 6.68–6.83 (m, 2H), 7.32–7.38 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 18.9, 22.9, 24.8, 49.4 (d, *J*_{C-P} = 10.9 Hz), 54.0, 56.9, 80.2, 86.3, 104.4, 110.8, 118.9, 132.0, 159.6, 162.9; IR (cm⁻¹) 3586, 3334, 2973, 2883, 1379. Anal. Calcd. for C₁₅H₂₀F₂NO₄P (347.11): C, 51.88; H, 5.80; N, 4.03 Found: C, 51.54; H, 5.56; N, 4.39.

4.2.4. Diethyl 1-methyl-3-phenylhexahydropyrrolo[1,2-c]oxazol-1-ylphosphonate **5d**

Colourless oil, (174 mg, 59%). ¹H NMR (400 MHz, CDCl₃) δ 0.84 (d, *J* = 17.3 Hz, 3H), 1.28–1.34 (m, 6H), 1.73–1.82 (m, 1H), 1.85–2.01 (m, 2H), 2.08–2.16 (m, 1H), 2.71–2.76 (m, 1H), 2.88–2.94 (m, 1H), 4.08–4.21 (m, 4H), 5.1 (dd, *J*₁ = 1.6 Hz, *J*₂ = 5.5 Hz, 1H), 5.22 (d, *J* = 13.6 Hz, 1H), 7.11–7.29 (m, 5H); ¹³C NMR (100 MHz, CDCl₃) δ 15.2, 15.8, 16.6, 25.2, 29.9, 47.1 (d, *J*_{C-P} = 11.9 Hz), 62.1 (d, *J*_{C-P} = 7.6 Hz), 62.9 (d, *J*_{C-P} = 7.5 Hz), 65.8, 83.1 (d, *J*_{C-P} = 10.0 Hz), 97.2, 126.6, 127.4, 127.9, 139.6; IR (cm⁻¹) 3566, 3332, 2972, 2882, 1456. Anal. Calcd. for C₁₇H₂₆N₂O₄P (339.16): C, 60.17; H, 7.72; N, 4.13

Found: C, 60.43; H, 7.91; N, 3.81.

4.2.5. Diethyl 1-methyl-3-(4-nitrophenyl)hexahydropyrrolo[1,2-c]oxazol-1-ylphosphonate **5e**

Colourless oil, (169 mg, 65%). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 0.83 (d, $J = 17.0$ Hz, 3H), 1.28–1.36 (m, 6H), 1.76–1.84 (m, 1H), 1.87–2.03 (m, 2H), 2.11–2.20 (m, 1H), 2.72–2.78 (m, 1H), 2.81–2.90 (m, 1H), 4.04–4.21 (m, 4H), 5.13 (dd, $J_1 = 1.5$ Hz, $J_2 = 5.5$ Hz, 1H), 5.29 (d, $J = 13.7$ Hz, 1H), 7.79 (dd, $J_1 = 8.8$ Hz, $J_2 = 251.4$ Hz, 4H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 14.2, 15.8, 16.6, 25.1, 29.8, 47.3 (d, $J_{C-P} = 11.0$ Hz), 62.6, 63.4, 65.2, 82.2 (d, $J_{C-P} = 11.0$ Hz), 97.6, 123.3, 127.4, 146.3, 147.3; IR (cm^{-1}) 3648, 3334, 2973, 2880, 1524. Anal. Calcd. for $\text{C}_{17}\text{H}_{25}\text{N}_2\text{O}_6\text{P}$ (384.15): C, 53.12; H, 6.56; N, 7.29 Found: C, 52.81; H, 6.83; N, 6.88.

4.2.6. Diisopropyl 1-methyl-3-(4-nitrophenyl)hexahydropyrrolo[1,2-c]oxazol-1-ylphosphonate **5f**

Colourless oil, (155 mg, 64%). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 0.82 (d, $J = 16.8$ Hz, 3H), 1.24–1.37 (m, 12H), 1.72–1.83 (m, 1H), 1.87–2.03 (m, 2H), 2.11–2.21 (m, 1H), 2.72–2.77 (m, 1H), 2.82–2.88 (m, 1H), 4.70–4.86 (m, 2H), 5.25 (dd, $J_1 = 1.6$ Hz, $J_2 = 6.4$ Hz, 1H), 5.31 (d, $J = 14.0$ Hz, 1H), 7.81 (dd, $J_1 = 8.8$ Hz, $J_2 = 11.2$ Hz, 4H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 16.0, 23.7 (d, $J_{C-P} = 0.1$ Hz, 2C), 24.1 (d, $J_{C-P} = 0.1$ Hz, 2C), 25.1, 29.8, 47.6 (d, $J_{C-P} = 11.7$ Hz), 65.3, 70.9 (d, $J_{C-P} = 18.1$ Hz), 72.2 (d, $J_{C-P} = 7.5$ Hz), 82.1 (d, $J_{C-P} = 11.9$ Hz), 97.7 (d, $J_{C-P} = 5.2$ Hz), 123.3, 127.4, 145.3, 147.5; IR (cm^{-1}) 3330, 2973, 2927, 2880, 1379. Anal. Calcd. for $\text{C}_{19}\text{H}_{29}\text{N}_2\text{O}_6\text{P}$ (412.18): C, 55.33; H, 7.09; N, 6.79 Found: C, 54.91; H, 6.78; N, 7.44.

4.2.7. Dimethyl 1-methyl-3-(4-nitrophenyl)tetrahydro-1H-oxazolo[3,4-c]thiazol-1-ylphosphonate **5g**

Yellow oil, (168 mg, 63%). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 0.93 (d, $J = 16.7$ Hz, 3H), 3.11 (dd, $J_1 = 4.4$ Hz, $J_2 = 12.9$ Hz, 1H), 3.29 (d, $J = 12.8$ Hz, 1H), 3.80 (t, $J = 10.4$ Hz, 6H), 3.99 (d, $J = 0.8$ Hz, 1H), 4.02 (d, $J = 0.7$ Hz, 1H), 5.21 (d, $J = 4.3$ Hz, 1H), 5.30 (d, $J = 11.1$ Hz, 1H), 7.52 (d, $J = 10.6$ Hz, 2H), 8.13 (d, $J = 9.2$ Hz, 2H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 13.0, 37.8, 53.3, 53.9, 65.7, 67.5, 82.0, 97.8 (d, $J_{C-P} = 0.1$ Hz), 123.1, 128.1, 143.7, 147.8; IR (cm^{-1}) 3566, 3335, 2973, 2883. Anal. Calcd. for $\text{C}_{14}\text{H}_{19}\text{N}_2\text{O}_6\text{PS}$ (374.07): C, 44.92; H, 5.12; N, 7.48 Found: C, 45.22; H, 5.38; N, 7.11.

4.2.8. Dimethyl 1-ethyl-3-(4-nitrophenyl)hexahydropyrrolo[1,2-c]oxazol-1-ylphosphonate **5h**

Colourless oil, (170 mg, 63%). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 0.79 (t, $J = 7.4$ Hz, 3H), 1.27 (m, 2H), 1.84–2.15 (m, 2H), 1.98 (m, 2H), 2.93 (m, 2H), 3.72–3.92 (m, 6H), 5.24 (d, $J = 5.6$ Hz, 1H), 5.34 (d, $J = 13.7$ Hz, 1H), 7.45 (d, $J = 8.7$ Hz, 2H), 8.11 (d, $J = 10.7$ Hz, 2H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 10.4, 24.7, 29.5, 31.4, 46.7, 53.1, 53.9, 70.2, 83.3, 97.9, 123.3, 127.9, 146.2, 147.4; IR (cm^{-1}) 3566, 3355, 2972, 2881, 1520. Anal. Calcd. for $\text{C}_{16}\text{H}_{23}\text{N}_2\text{O}_6\text{P}$ (370.13): C, 51.89; H, 6.26; N, 7.46 Found: C, 51.52; H, 5.88; N, 7.11.

4.2.9. Dimethyl 1-ethyl-3-(4-nitrophenyl)tetrahydro-1H-oxazolo[3,4-c]thiazol-1-ylphosphonate **5i**

Yellow oil, (157 mg, 61%). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 0.86 (t, $J = 7.4$ Hz, 3H), 1.06 (m, 2H), 3.10 (m, 2H), 3.74 (d, $J = 5.4$ Hz, 1H), 3.80 (d, $J = 11.4$ Hz, 6H), 4.05 (d, $J = 11.3$ Hz, 1H), 4.78 (d, $J = 12.9$ Hz, 1H), 5.30 (d, $J = 4.8$ Hz, 1H), 7.69 (d, $J = 8.5$ Hz, 2H), 8.11 (d, $J = 8.7$ Hz, 2H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 7.9, 8.9, 39.7, 54.1, 58.2, 70.4, 85.7, 87.4, 98.2, 123.6, 129.7, 144.1, 147.7; IR (cm^{-1}) 3648, 3333, 2973, 2882, 1456. Anal. Calcd. for $\text{C}_{15}\text{H}_{21}\text{N}_2\text{O}_6\text{PS}$ (388.09): C, 46.39; H, 5.45; N, 7.21 Found: C, 46.02; H, 5.24; N, 7.02.

4.2.10. Dimethyl 1-isopropyl-3-(4-nitrophenyl)hexahydropyrrolo[1,2-c]oxazol-1-ylphosphonate **5j**

Colourless oil, (161 mg, 62%). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 1.19 (t, $J = 7.1$ Hz, 6H), 1.47 (m, 1H), 1.80 (m, 2H), 2.13 (m, 1H), 2.83 (m, 2H), 3.11 (m, 1H), 3.78 (m, 6H), 5.19 (d, $J = 9.0$ Hz, 1H), 5.56 (d, $J = 2.4$ Hz, 1H), 7.35 (d, $J = 7.1$ Hz, 2H), 7.96 (d, $J = 6.4$ Hz, 2H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 12.4, 19.20, 21.74, 22.44, 27.94, 50.62, 52.81, 69.57, 121.56, 125.07, 126.35, 128.28, 129.35, 142.07, 147.23; IR (cm^{-1}) 3649, 3334, 2973, 2881, 1455. Anal. Calcd. for $\text{C}_{17}\text{H}_{25}\text{N}_2\text{O}_6\text{P}$ (384.15): C, 53.12; H, 6.56; N, 7.29 Found: C, 52.88; H, 6.23; N, 7.01.

4.2.11. Dimethyl 1-isopropyl-3-(3-nitrophenyl)hexahydropyrrolo[1,2-c]oxazol-1-ylphosphonate **5k**

Colourless oil, (164 mg, 63%). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 1.26 (t, $J = 7.1$ Hz, 6H), 1.47–1.69 (m, 1H), 1.81–1.90 (m, 2H), 1.95–2.06 (m, 1H), 2.30–2.42 (m, 2H), 2.57 (pd, $J_1 = 13.9$ Hz, $J_2 = 6.9$ Hz, 1H), 3.78–3.91 (m, 6H), 5.30 (dd, $J_1 = 8.7$ Hz, $J_2 = 5.7$ Hz, 1H), 5.64 (d, $J = 3.3$ Hz, 1H), 7.21–8.12 (m, 4H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 12.45, 20.20, 21.75, 22.44, 25.87, 50.62, 52.81, 69.57, 121.56, 125.07, 126.35, 128.28, 129.35, 145.77, 147.23; IR (cm^{-1}) 3650, 3334, 2974, 2882, 1455. Anal. Calcd. for $\text{C}_{17}\text{H}_{25}\text{N}_2\text{O}_6\text{P}$ (384.15): C, 53.12; H, 6.56; N, 7.29 Found: C, 52.98; H, 6.24; N, 7.14.

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