A New Approach to the Synthesis of 3-Substituted 4-(Diethoxyphosphoryl)isoxazoles from 3-Azidoalka-1,3-dienylphosphonates

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Abstract: New 3-azidoalka-1,3-dienylphosphonates were synthesized by a convenient and efficient method. These compounds are useful as intermediates in the preparation of 3-(3-aryl-4,5-dihydroisoxazol-5-yl)- and 3-alkenyl-4-(diethoxyphosphoryl)isoxazoles.

Key words: allenes, azides, isoxazoles, nitrile oxides, phosphorus

A 3,4-disubstituted isoxazole scaffold has frequently been incorporated into the pharmacophore design for a wide range of pharmaceutical agents.1 Some examples include nonsteroidal anti-inflammatory drugs (NSAIDs),2 protein kinase inhibitors,3 hypertensive agents.4 Isoxazole derivatives form a part of many drugs used for antidepressant therapy and the treatment osteoarthritis or rheumatoid arthritis.5,6 The introduction of different functional groups in the 3,4-positions of the isoxazole ring, makes it possible to expand the range reactions of 3,4-disubstituted isoxazoles7,8 and to study their biological properties and, in this context, the synthesis of 3-(3-aryl-4,5-dihydroisoxazol-5-yl)- and 3-alkenyl-4-(diethoxyphosphoryl)isoxazoles is of interest. However, this type of isoxazole has not previously been described in the literature.

As part of our research on the use of allenes as versatile starting materials in organic synthesis9 we recently reported their application to the synthesis of 2-(diethoxyphosphoryl)-3-(3-phenyl-4,5-dihydroisoxazol-5-yl)-2H-azirines.10 In conjunction with our continuing study of the chemical properties of polyfunctional alkadienylphosphonates and the design of new phosphonoheterocycles, we turned our attention towards development of synthesis 3-substituted 4-(diethoxyphosphoryl)isoxazoles by using phosphonoallenes as starting materials.

General retrosynthetic analysis, illustrated for the synthesis of target compounds 7 and 8, is given in Scheme 1. It revealed that the 3,4-disubstituted isoxazoles might be constructed by a simple and efficient three-step procedure involving preparation of alkenols 1, their transformation to 3-azidoalka-1,3-dienylphosphonates 5, synthesis of 4,5-dihydroisoxazolyl derivatives 6, and cyclization of 5 and 6 to give the final 3,4-disubstituted isoxazoles 7 and 8. The propargyl alcohols 1 were prepared in 80% yields by a standard procedure,11 starting from O-protected propargylic alcohol by using ethyl vinyl ether.12 Phosphorylated allenes 3 were synthesized directly from propargylic alcohols 1 in ~70% yield by Horner–Mark [2,3]-sigmatropic rearrangement of the unstable phosphates 213 (Scheme 2, Table 1). The treatment of compounds 3 with a methanol solution in the presence of 4-toluenesulfonic acid afforded unprotected allenic alcohols 4 in quantitative yields.

The reaction of phosphonates 4 with sodium azide at 40–50 °C for two hours in N,N-dimethylformamide lead to the formation of alka-1,3-dienes 5 with an E-double bond configuration. Compounds 5 were isolated by flash chromatography on silica gel in 73–80% yields. Confirmation of the E-structure of 3-azidoalka-1,3-dienes 5 was established on the basis of their 1H and 13C NMR spectra. The signals of H2 in 5 appears at the lowest field of the alkadienyl isoxazolyl-1,3-dienes as a broad doublet at δ = 6.61–6.92, coupled to phosphorus (JH2,P = 1.8 Hz, only for 5a) as well as H1 (JH1,H1trans = 16.0–18.0 Hz). The signals of H1 in 5

Table 1 Yields of Compounds 4–8

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The quaternary C4, which carries the nitrile oxides leading to 4,5-dihydroisoxazoles 7 and 8 are stable compounds and were isolated by column chromatography on silica gel. The structural identity of isoxazole 7 and 8 was established by their 1H and 13C NMR spectra.

In summary, we have described an easy and convenient method for the preparation of new, synthetically valuable 3-(3-aryl-4,5-dihydroisoxazol-5-yl)- and 3-alkenyl-4-(diethoxyphosphoryl)isoxazoles from 3-azidoalka-1,3-dienylphosphonates. Further studies on the reactivity of 3-substituted 4-(diethoxyphosphoryl)isoxazoles and new derivatives are currently in progress.

NMR spectra were recorded on a Bruker CXP-200 spectrometer at 200 MHz (1H NMR), 81.01 MHz (31P NMR) and 50.3 MHz (13C NMR). The 1H NMR spectra were referenced to TMS as internal standard, the 31P NMR relative to external 85% H3PO4 in H2O. Benzaldehyde oximes are commercially available.

Details of the synthesis 5-chloro-2-(diethoxyphosphoryl)pent-2,3-dien-1-ol (4a), and 3-azido-2-(diethoxyphosphoryl)pent-2,4-dien-1-ol (5a) have been described in previous papers.10

5-Chloro-2-(diethoxyphosphoryl)hexa-2,3-dien-1-ol (4b)
Following the typical procedure for 4a using 1b (2.2 g, 0.01 mol), anhyd Et2O (90 mL), Et3N (1.52 g, 0.015 mol), and diethyl chloroformate (1.56 g, 0.01 mol) followed by column chromatography (CHCl3–MeOH, 20:1) gave 4b (1.93 g, 72%) as an oil; Rf = 0.3.

1H NMR (200 MHz, CDCl3): δ = 5.80 (dd, JH,P = 7.0 Hz, JCR = 2.0 Hz, JCR = 12.0 Hz, 2 H, CH2OH), 4.67 (ddq, JH,P = 7.0 Hz, JCR = 2.0 Hz, JCR = 12.0 Hz, 2 H, CH2OH), 1.68 (d, JCR = 7.0 Hz, 3 H, CH3), 1.38 (t, JCR = 7.0 Hz, 6 H, 2 POCH2CH3).

13C NMR (CDCl3): δ = 206.6 (d, JC,P = 5.0 Hz, CH2OH), 199.04 (d, JC,P = 206.6 Hz, =C=), 100.73 (d, JC,P = 5.0 Hz, =C=), 99.04 (d, JC,P = 185.0 Hz, =C), 63.4 (d, JC,P = 5.0 Hz, CH2OH), 63.2 (d, JC,P = 6.0 Hz, POCH2CH3). 1H NMR (81.01 MHz, CDCl3): δ = 16.65 (d, JC,P = 15.0 Hz, = CH), 4.67 (dq, JH,P = 11.0 Hz, 1 H, =CH), 4.67 (ddq, JH,P = 12.0 Hz, 2 H, =CH2), 1.50 (m, 2 H, CH2), 1.27 (t, JCH3 = 7.0 Hz, 6 H, 2 POCH2CH3).

31P NMR (81.01 MHz, CDCl3): δ = 16.02.

The next stage of our research entailed the synthesis of 4,5-dihydroisoxazoles from 3-azido-2-(diethoxyphosphoryl)penta-1,3-dien-5-ol (5a). The [3+2] cycloaddition of the nitrile oxides to 5a was performed in diethyl ether at −40 °C. In the optimized procedure, a solution of triethylamine in diethyl ether was added dropwise over two hours to the mixture of arylhydroximoyl chloride and dipolarophile 5a. 1,3-Diene 5a reacted smoothly with nitrile oxides leading to 4,5-dihydroisoxazoles 6a–e in yields of ca. 70–85%. Only the terminal double bond of alka-1,3-diene 5a reacts with arylnitrile oxides; the diethoxyphosphoryl-substituted double bond does not react with arylnitrile oxides.

The final step of the reaction of phosphonates 5 and 6 with manganese dioxide at room temperature leads to formation of 3,4-disubstituted isoxazoles 7 and 8. The progress of condensation was monitored by TLC on silica gel. In-
oil; Hz, =CN3), 141.00 (d, J = 148.64 Hz, =CP), 62.38 (d, J = 148.72 Hz, 1H, C), 100.31 (d, J = 148.72 Hz, 1H, CH), 33.06 (s, CH2), 31.21 (s, CH2), 22.56 (s, CH2), 16.65 (d, J = 6.0 Hz, 2POCH2CH3), 14.24 (s, CH3).

3-Phenyl-2-(diethoxyporphoryl)alka-2,4-diene-1-ol (5c)
Following the typical procedure for 5a using 4c (2.96 g, 0.01 mol) and NaN3 (1.63 g, 0.025 mol) followed by column chromatography (CHCl3–MeOH, 10:1) gave 5c (2.58 g, 80%) as an oil; Rf = 0.48.

3-Phenyl-2-(diethoxyporphoryl)octa-2,4-diene-1-ol (5e)
Following the typical procedure for 5a using 4c (2.96 g, 0.01 mol) and NaOH (1.05 g, 0.025 mol) followed by column chromatography (CHCl3–MeOH, 10:1) gave 5e (2.5 g, 79%) as an oil; Rf = 0.45.

3-Phenyl-2-(diethoxyporphoryl)octa-2,4-diene-1-ol (5f)
Following the typical procedure for 5a using 4c (2.96 g, 0.01 mol) and NaOH (1.05 g, 0.025 mol) followed by column chromatography (CHCl3–MeOH, 10:1) gave 5f (2.6 g, 81%) as an oil; Rf = 0.45.

3-Phenyl-2-(diethoxyporphoryl)octa-2,4-diene-1-ol (5g)
Following the typical procedure for 5a using 4c (2.96 g, 0.01 mol) and NaOH (1.05 g, 0.025 mol) followed by column chromatography (CHCl3–MeOH, 10:1) gave 5g (2.8 g, 82%) as an oil; Rf = 0.45.
5-[1-Azido-2-(diethoxyphosphoryl)-3-hydroxyprop-1-enyl]-3-(4-chlorophenyl)-4,5-dihydroisoaxazole (6c)

Following the typical procedure for 6a using 5a (0.261 g, 0.001 mol), 4-MeOCH₂CH₂Cl=NOH (0.254 g, 0.0015 mol), and Et₂N (0.303 g, 0.003 mol) followed by column chromatography (CHCl₃-MeOH: 1:1) to give 6c (0.335 g, 82%) as an oil; Rf = 0.57.

1H NMR (200 MHz, CDCl₃): δ = 7.72–7.68 (m, 2 H, H₂CH₂), 7.28–7.24 (m, 2 H, H₂CH₂), 6.23 (dt, J₁=11.0 Hz, J₂=1.5 Hz, 1 H, OCH), 4.32 (d, J₁=16.0 Hz, 2 H, CH₂OH), 4.16–4.00 (m, 4 H, 2 POCH₂CH₃), 3.86 (AB, J₁=12.0 Hz, J₂=7.0 Hz, 1 H, CH₂), 3.40 (AB, J₁=9.0 Hz, J₂=7.0 Hz, 1 H, CH₂), 3.02 (br s, 1 H, OH), 2.40 (s, 3 H, CH₃), 1.38 (t, J₁=7.0 Hz, 6 H, 2 POCH₂CH₃)

13C NMR (50.3 MHz, CDCl₃): δ = 156.80 (s, C=CH), 148.87 (d, J₁=25.0 Hz, =CH₃), 140.10 (s, CH₂), 129.55 (s, C₆H₅), 126.70 (s, C₁₀H₅), 126.03 (s, C₁₀H₅), 118.10 (d, J₁=185.2 Hz, =CH₃), 79.18 (d, J₁=5.0 Hz, CH₀), 62.71 (d, J₁=6.0 Hz, POCH₂CH₃), 62.50 (d, J₁=5.0 Hz, POCH₂CH₃), 59.03 (d, J₁=5.0 Hz, CH₂O), 40.53 (s, CH₂), 21.38 (s, CH₂), 16.42 (d, J₁=7.0 Hz, 2 POCH₂CH₃)

13P NMR (81.01 MHz, CDCl₃): δ = 19.89.

13P NMR (81.01 MHz, CDCl₃): δ = 16.65.
Following the typical procedure for 7a using 5d (0.318 g, 0.001 mol), MnO₂ (1.00 g), and CHCl₃ (10 mL), followed by column chromatography (CHCl₃) gave 7d (0.224 g, 79%) as an oil; Rₜ = 0.63.

1H NMR (200 MHz, CDCl₃); δ = 8.72 (d, J_H,P = 1.5 Hz, 1 H, =CHO), 6.87 (d, J_H,P = 6.8 Hz, J_H,J_H = 16.3 Hz, 1 H, =CH(CH₃)), 6.43 (br d, J_H,J_H = 16.3 Hz, 1 H, =CH), 4.27–4.06 (m, 4 H, 2 POCH₂CH₃), 3.31 (s, CH₃), 1.80 (d, J_H,P = 7.0 Hz, 7H, PO(CH₃)), 1.39 (t, J_H,J_H = 7.0 Hz, 6 H, 2 POCH₂CH₃), 0.95 (t, J_H,J_H = 6.8 Hz, 3 H, CH₃).

13C NMR (50.3 MHz, CDCl₃); δ = 166.72 (d, J_C,P = 23.0 Hz, =CHO), 160.00 (d, J_C,P = 12.0 Hz, C=CN), 142.49 (s, =CH), 115.71 (s, =CH), 107.38 (d, J_C,P = 16.0 Hz, PC=), 63.00 (d, J_C,P = 6.0 Hz, 2 POCH₂CH₃), 33.44 (s, CH₃), 31.08 (s, CH₃), 22.60 (s, CH₂), 16.72 (d, J_C,P = 7.0 Hz, 2 POCH₂CH₃), 14.29 (s, CH₃).

1P NMR (81.01 MHz, CDCl₃); δ = 0.0.


4-(Diethoxymethyl)-3-(hex-1-enyl)isoxazole (7d)

Following the typical procedure for 7a using 6a (0.38 g, 0.001 mol), MnO₂ (1.00 g), and CHCl₃ (10 mL), followed by column chromatography (CHCl₃) gave 8a (0.82 g, 80%) as an oil; Rₜ = 0.48.

1H NMR (200 MHz, CDCl₃); δ = 8.75 (d, J_H,P = 1.5 Hz, 1 H, =CHO), 7.42–7.69 (m, 2 H, H₄), 7.44–7.41 (m, 1 H, H₃), 6.01 (dd, J_H,J_H = 11.0 Hz, J_H,J₄ = 7.4 Hz, 1 H, OCH), 4.32–4.15 (m, 4 H, 2 POCH₂CH₃), 4.03 (AB, J_H,J₄ = 11.0 Hz, J₄,J₅ = 17.0 Hz, 1 H, CH₃(CH₂)), 3.69 (AB, J_H,J₄ = 7.4 Hz, J₄,J₅ = 17.0 Hz, 1 H, CH₂), 1.39 (t, J_H,J₄ = 7.0 Hz, 3 H, POCH₂CH₃), 1.35 (t, J_H,J₄ = 7.0 Hz, 3 H, POCH₂CH₃).

1C NMR (50.3 MHz, CDCl₃); δ = 166.43 (d, J_C,P = 22.0 Hz, =CHO), 160.35 (d, J_C,P = 13.0 Hz, C=CN), 157.36 (s, C₆), 130.86 (s, C₅), 129.27 (s, C₄), 127.37 (s, C₃), 108.69 (d, J_C,P = 218.0 Hz, PC=), 74.21 (s, CH=O), 63.45 (d, J_C,P = 6.0 Hz, 2 POCH₂CH₃), 39.54 (s, CH₃), 16.76 (d, J_C,P = 7.0 Hz, POCH₂CH₃), 16.69 (d, J_C,P = 7.0 Hz, POCH₂CH₃), 21.38 (s, CH₃).

1P NMR (81.01 MHz, CDCl₃); δ = 15.3.


4-(Diethoxymethyl)-3-(3-phenyl-4,5-dihydroisoxazol-5-yl)-isonicotazole (7d)

Following the typical procedure for 7a using 6a (0.38 g, 0.001 mol), MnO₂ (1.00 g), and CHCl₃ (10 mL), followed by column chromatography (CHCl₃) gave 8d (0.224 g, 79%) as an oil; Rₜ = 0.48.

1H NMR (200 MHz, CDCl₃); δ = 8.70 (d, J_H,J₄ = 2.0 Hz, 1 H, =CHO), 7.70–7.77 (m, 2 H, H₄), 7.29–7.26 (m, 2 H, H₃), 6.12 (dd, J_H,J_H = 12.0 Hz, J_H,J₄ = 7.0 Hz, 1 H, OCH), 4.25–4.10 (m, 4 H, 2 POCH₂CH₃), 4.08 (AB, J_H,J₄ = 12.0 Hz, J₄,J₅ = 17.0 Hz, 1 H, CH₃(CH₂)), 3.49 (AB, J_H,J₄ = 7.0 Hz, J₄,J₅ = 17.0 Hz, 1 H, CH₂), 2.43 (s, 3 H, CH₃), 1.30 (t, J_H,J₄ = 7.0 Hz, 3 H, POCH₂CH₃), 1.35 (t, J_H,J₄ = 7.0 Hz, 3 H, POCH₂CH₃).

1C NMR (50.3 MHz, CDCl₃); δ = 166.83 (d, J_C,P = 22.0 Hz, =CH=O), 161.55 (d, J_C,P = 13.0 Hz, C=CN), 140.41 (s, C₆), 129.65 (s, C₅), 126.78 (s, C₄), 126.13 (s, C₃), 107.54 (d, J_C,P = 218.5 Hz, PC=), 74.67 (s, CH=O), 63.54 (d, J_C,P = 6.0 Hz, 2 POCH₂CH₃), 39.56 (s, CH₃), 16.76 (d, J_C,P = 7.0 Hz, POCH₂CH₃), 21.38 (s, CH₃), 16.43 (d, J_C,P = 7.0 Hz, POCH₂CH₃).

1P NMR (81.01 MHz, CDCl₃); δ = 12.5.


4-(Diethoxymethyl)-3-(3-(4-fluorophenyl)-4,5-dihydroisoxazol-5-yl)-isonicotazole (8e)

Following the typical procedure for 7a using 6a (0.372 g, 0.001 mol), MnO₂ (1.00 g), and CHCl₃ (10 mL), followed by column chromatography (CHCl₃) gave 8e (0.319 g, 84%) as an oil; Rₜ = 0.48.

1H NMR (200 MHz, CDCl₃); δ = 8.75 (d, J_H,J₄ = 2.0 Hz, 1 H, =CHO), 7.78–7.54 (m, 2 H, H₄), 7.28–7.15 (m, 2 H, H₃), 6.18 (dd, J_H,J_H = 12.0 Hz, J_H,J₄ = 7.0 Hz, 1 H, OCH), 4.22–4.14 (m, 4 H, 2 POCH₂CH₃), 4.06 (AB, J_H,J₄ = 12.0 Hz, J₄,J₅ = 17.0 Hz, 1 H, =CH=O), 7.42–7.34 (m, 5 H, Carom), 110.73 (d, J_C,P = 17.0 Hz, C₆), 109.92 (d, J_C,P = 219.3 Hz, PC=), 74.52 (s, CH=O), 62.67 (d, J_C,P = 6.0 Hz, 2 POCH₂CH₃), 39.83 (s, CH₃), 16.52 (d, J_C,P = 7.0 Hz, POCH₂CH₃), 16.76 (d, J_C,P = 7.0 Hz, POCH₂CH₃), 21.38 (s, CH₃), 16.43 (d, J_C,P = 7.0 Hz, POCH₂CH₃).

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\( \text{CHH}, 3.84 \text{ (s, 3 H, OCH}_3 \text{)}, 3.43 \text{ (AB, } J_{\text{H,H}} = 7.0 \text{ Hz, } J_{\text{H,P}} = 17.0 \text{ Hz, 1 H, CHH}), 1.29 \text{ (s, } J_{\text{H,H}} = 7.0 \text{ Hz, 3 H, POCH}_2\text{CH}_3 \text{), 1.31 \text{ (s, } J_{\text{H,H}} = 7.0 \text{ Hz, 3 H, POCH}_2\text{CH}_3 \text{)} \)

\( ^{13}\text{C NMR (50.3 MHz, CDCl}_3 \): } \delta = 166.64 \text{ (d, } J_{\text{C,P}} = 22.0 \text{ Hz, =CHO), 161.55 \text{ (d, } J_{\text{C,P}} = 12.5 \text{ Hz, C=N), 137.50 \text{ (s, } C_{\text{arom)}, 128.67 \text{ (s, } C_{\text{arom)}, 126.96 \text{ (s, } C_{\text{arom), 127.22 \text{ (s, } C_{\text{arom), 107.74 \text{ (d, } J_{\text{C,P}} = 218.0 \text{ Hz, PC=), 74.82 \text{ (s, CH–O), 63.76 \text{ (d, } J_{\text{C,P}} = 6.0 \text{ Hz, 2 POCH}_2\text{CH}_3 \text{), 55.8 \text{ (s, OCH}_3 \text{), 39.26 \text{ (s, CH}_3 \text{), 16.82 \text{ (d, } J_{\text{C,P}} = 7.0 \text{ Hz, POCH}_2\text{CH}_3 \text{), 16.43 \text{ (d, } J_{\text{C,P}} = 7.0 \text{ Hz, POCH}_2\text{CH}_3 \text{).} \)

\( ^{31}\text{P NMR (81.01 MHz, CDCl}_3 \): } \delta = 14.0. \)


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References


