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LETTERS TO THE EDITOR

Heterocyclization Reaction of Chloroacetylenephosphonates with 2-Acylamidomalonates into 5-(Dialkoxyphosphorylmethylidene)oxazolines

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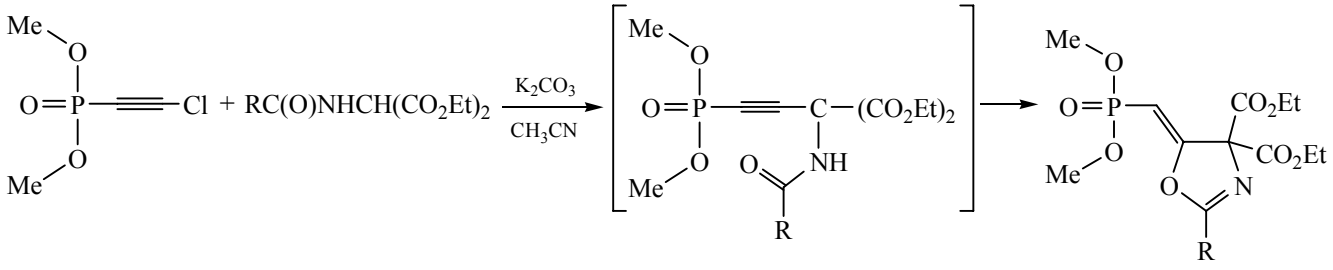
Oxazoline structure and its pharmacophore properties are well known [1]. Generally, oxazoline ring is formed in the reaction of carbonyl compounds with iminomalonates [2, 3] and nitriles [4]. Literature and patent data exist on the synthesis of oxazoline ring through the heterocyclization of acetylene amides in the presence of various catalysts [5, 6].

There is no information up to date on obtaining phosphorylated oxazolines, although it can be assumed that the introduction of the phosphorus-containing moiety into the oxazoline ring can expand the range of biological activity of these compounds.

We found that the reaction of dimethyl chloroacetylenephosphonate with amidomalonates in anhydrous acetonitrile in the presence of potassium carbonate at room temperature results in the new class of compounds, namely, phosphorylated oxazolines. The reaction proceeds as a 2-*C*-alkynylation of amidomalonates further involving the triple bond of the assumed intermediate **A** into the heterocyclization. The intermediate **A** formed by the replacement of the chlorine atom in chloroacetylenephosphonate with acetamidomalonate residue has two nucleophilic sites, carbonyl and amine groups of the amide fragment. The interaction of these sites with an acetylene bond can lead to the formation of oxazoline or aziridine structure, respectively. The reaction was shown to give rise to 2-substituted 4,4-bis(ethoxycarbonyl)-5-(dimethoxyphosphorylidene)-1,3-oxazolines **I**–**V** in 80–90% yields.

The reaction proceeds quite stereoselectively to form oxazolines **I**–**V** as a mixture of *Z*,*E*-isomers in a ratio of 10:1. In the ^{1}H NMR spectra of the compounds there are the characteristic doublets of the olefinic protons: a strong doublet at ~ δ 5.4–5.5 ppm ($^2J_{HP}$ 7.6 Hz) of the *Z*-isomer and a doublet of low intensity in a weaker field at ~ δ 5.6–5.7 ppm ($^2J_{HP}$ ~ 5 Hz) of the *E*-isomer. The ^{31}P NMR spectra also contain two signals with an intensity ratio of 10:1 at 15–17 ppm. The major *Z*-isomers of oxazolines **I**–**V** were isolated by the recrystallization from a petroleum ether–methylene chloride mixture. Their configuration (the *cis*-arrangement of dimetoxyphosphoryl group and the oxazoline oxygen atom relative to the exocyclic double



A **I**–**V** (*Z*:*E* 10:1)

R = Me (**I**); Ph (**II**), *p*-MePh (**III**), *p*-ClPh (**IV**), *p*-NO_2Ph (**V**).

bond) was confirmed by the X-ray analysis of oxazoline **IV** (CCDC 847497).

The ^{13}C NMR spectra of *Z*-oxazolines **I**–**V** contain the characteristic signals of ethylene carbon atoms: an intensive doublet at δ_C 90 ppm with a characteristic large spin-spin coupling constant $^1J_{CP}$ 180–190 Hz, a slightly split doublet signal of low intensity of the second carbon atom at δ_C 160 ppm, and a signal of the malonate tetrasubstituted carbon atom in oxazoline ring at δ_C 80 ppm with a characteristic constant $^3J_{CP}$ 7–13 Hz. The signal of the carbon atom of the C=N fragment in the oxazoline ring is shifted downfield and appears as a singlet at δ_C 164 ppm. The spectra of oxazoline **IV** taken in a ^{13}C–^1H coupling mode and a DEPT experiment confirm this assignment. The ESI mass spectrum of oxazoline **IV** contains a single signal with *m*/*z* 445.37 $[M]^+$.

2-Methyl-4,4-bis(ethoxycarbonyl)-5-dimethoxyphosphorylmethylidene-1,3-oxazoline (I). To a mixture of 0.5 g (3 mmol) of dimethyl chloroacetylenephosphonate and 0.81 g (6 mmol) of powdered anhydrous potassium carbonate in 10 ml of anhydrous acetonitrile was added 0.66 g (3 mmol) of diethyl 2-acetamidomalonate. The reaction was carried out at room temperature with vigorous stirring for 16 h. Then the inorganic precipitate was centrifuged off, and the solvent was removed in a vacuum. Yield 1.01 g (85%), viscous dark red liquid. ^1H NMR spectrum, δ, ppm: *Z*-isomer, 1.1 t (6H, CH_3, $^3J_{HH}$ 6.8 Hz), 2.09 s (3H, CH_3), 3.56 d (6H, OCH_3, $^3J_{HP}$ 11.2 Hz), 4.27 d.q (4H, OCH_2, $^3J_{HH}$ 6.8 Hz), 5.22 d (1H, CH, $^2J_{HP}$ 7.6 Hz); *E*-isomer, 5.32 d (1H, CH, $^2J_{HP}$ 5.2 Hz). ^{13}C NMR spectrum, δ_C, ppm: 13.16 (CH_3), 13.28 ($CH_2\underline{CH_3}$), 51.89 d (OCH_3, $^2J_{CP}$ 5.8 Hz), 62.87 (OCH_2), 83.91 d (C^3, $^3J_{CP}$ 11.9 Hz), 90.73 d (C^1, $^1J_{CP}$ 189.8 Hz), 164.54 (C=O), 166.76 (C^4). ^{31}P NMR spectrum, δ_P, ppm: 13.95 (*Z*-isomer), 17.84 (*E*-isomer).

2-Phenyl-4,4-bis(ethoxycarbonyl)-5-dimethoxyphosphorylmethylidene-1,3-oxazoline (II) was obtained similarly from 0.5 g (3 mmol) of dimethyl chloroacetylenephosphonate, 0.81 g (6 mmol) of powdered anhydrous potassium carbonate, and 0.54 g (3 mmol) of diethyl 2-benzamidomalonate. Yield 1.1 g (89%). ^1H NMR spectrum, δ, ppm: *Z*-isomer, 1.28 t (6H, CH_3, $^3J_{HH}$ 7.6 Hz), 3.78 d (6H, OCH_3, $^3J_{HP}$ 11.2 Hz), 4.28 q and 4.29 q (4H, OCH_2, $^3J_{HH}$ 7.6 Hz), 5.52 d (1H, CH, $^2J_{HP}$ 7.2 Hz), 7.45 t (2H, *m*-Ph, $^3J_{HH}$ 7.8 Hz), 7.56 t (1H, *p*-Ph, $^3J_{HH}$ 7.8 Hz), 8.08 d (2H, *o*-Ph, $^3J_{HH}$ 7.8 Hz); *E*-isomer, 5.67 d (1H, CH, $^2J_{HP}$ 5.2 Hz). ^{13}C NMR spectrum, δ_C, ppm: 13.70 (CH_3), 52.36 br.s (CH_3O), 63.23 (OCH_2), 84.33 d (C^3, $^3J_{CP}$ 6.5 Hz), 91.36 d (C^1, $^1J_{CP}$ 190.9 Hz), 124.63 (*ipso*-Ph), 126.63 (*m*-Ph), 128.98 (*o*-Ph), 133.16 (*p*-Ph), 161.81 (C^2), 164.62 (C=O), 165.26 (C^4). ^{31}P NMR spectrum, δ_P, ppm: 15.1 (*Z*-isomer), 17.8 (*E*-isomer).

2-(*p*-Methylphenyl)-4,4-bis(ethoxycarbonyl)-5-dimethoxyphosphorylmethylidene-1,3-oxazoline (III) was obtained similarly from 0.5 g (3 mmol) of dimethyl chloroacetylenephosphonate, 0.81 g (6 mmol) of powdered anhydrous potassium carbonate, and 0.61 g (3 mmol) of diethyl 2-(3-methylbenzamido)malonate. Yield 0.7 g (82%). ^1H NMR spectrum, δ, ppm: *Z*-isomer, 1.25 t (6H, CH_3, $^3J_{HH}$ 7.0 Hz), 2.3 (3H, CH_3), 3.74 d (6H, OCH_3, $^3J_{HP}$ 11.0 Hz), 4.26 q (4H, OCH_2, $^3J_{HH}$ 7.0 Hz), 5.46 d (1H, CH, $^2J_{HP}$ 7.2 Hz), 7.21 d (2H, *m*-Ph, $^3J_{HH}$ 7.6 Hz), 7.93 d (2H, *o*-Ph, $^3J_{HH}$ 7.6, $^4J_{HH}$ 2.8 Hz); *E*-isomer, 5.61 d (1H, CH, $^2J_{HP}$ 5.2 Hz). ^{13}C NMR spectrum, δ_C, ppm: 13.68 (CH_3), 21.49 (CH_3), 52.32 d (OCH_3, $^2J_{CP}$ 5.4 Hz), 63.16 (OCH_2), 84.25 d (C^3, $^3J_{CP}$ 9.1 Hz), 92.05 d (C^1, $^1J_{CP}$ 192.3 Hz), 121.82 (*ipso*-Ph), 128.95 (*o*-Ph), 129.31 (*m*-Ph), 144.04 (*ipso*-CH_3-Ph), 161.95 (C^2), 164.69 (C=O), 165.31 (C^4). ^{31}P NMR spectrum, δ_P, ppm: 14.9 (*Z*-isomer), 18.1 (*E*-isomer).

2-(*p*-Chlorophenyl)-4,4-bis(ethoxycarbonyl)-5-dimethoxyphosphorylmethylidene-1,3-oxazoline (II) was obtained similarly from 0.5 g (3 mmol) of dimethyl chloroacetylenephosphonate, 0.81 g (6 mmol) of powdered anhydrous potassium carbonate, and 0.9 g (3 mmol) of diethyl 2-(4-chlorobenzamido)malonate. The products were isolated by the recrystallization from water. Yield 1.1 g (82%), mp 120°C (water). ^1H NMR spectrum, δ, ppm: *Z*-isomer, 1.31 t (6H, CH_3, $^3J_{HH}$ 7.5 Hz), 3.79 d (6H, OCH_3, $^3J_{HP}$ 11.2 Hz), 4.32 q and 4.34 q (4H, OCH_2), 5.54 d (1H, CH, $^2J_{HP}$ 6.4 Hz), 7.45 d (2H, *o*-Ph, $^3J_{HH}$ 8.0 Hz), 8.04 d (2H, *m*-Ph, $^3J_{HH}$ 8.0 Hz). ^{13}C NMR spectrum, δ_C, ppm: 13.64 (CH_3), 52.33 d (OCH_3, $^2J_{CP}$ 5.5 Hz), 63.22 (OCH_2), 84.15 d (C^3, $^3J_{CP}$ 13 Hz), 91.67 d (C^1, $^1J_{CP}$ 188.1 Hz), 123.09 (*ipso*-Ph), 128.97 (*m*-Ph), 130.66 (*o*-Ph), 139.66 (*ipso*-Cl-Ph), 161.71 d (C^2, $^2J_{CP}$ 3.0 Hz), 164.39 (C^4), 164.39 (C=O). ^{31}P NMR spectrum, δ_P, ppm: 14.5 (*Z*-isomer), 17.9 (*E*-isomer).

2-(*p*-Nitrophenyl)-4,4-bis(ethoxycarbonyl)-5-dimethoxyphosphorylmethylidene-1,3-oxazoline (II) was obtained similarly from 0.5 g (3 mmol) of dimethyl chloroacetylenephosphonate, 0.81 g (6 mmol) of powdered anhydrous potassium carbonate, and

0.64 g (3 mmol) of diethyl 2-(3-nitrobenzamido)malonate. Yield 0.88 g (96%). ^{1}H NMR spectrum, δ, ppm: *Z*-isomer, 1.28 t (6H, CH_3, $^3J_{HH}$ 7.2 Hz), 3.66 d (6H, OCH_3, $^3J_{HP}$ 12 Hz), 4.29 q (4H OCH_2, $^3J_{HH}$ 7.2 Hz), 5.56 d (1H, CH, $^2J_{HP}$ 6.4 Hz), 8.29 d and 8.30 d (4H, Ph, $^3J_{HH}$ 8 Hz); *E*-isomer, 5.74 d (1H, CH, $^2J_{HP}$ 5.3 Hz). ^{13}C NMR spectrum, δ_C, ppm: 13.68 (CH_3), 52.47 d (OCH_3, $^2J_{CP}$ 5.3 Hz), 63.54 (OCH_2), 84.28 d (C^3, $^3J_{CP}$ 9.1 Hz), 92.61 d (C^1, $^1J_{CP}$ 190 Hz), 123.7 (*m*-Ph), 130.16 (*o*-Ph), 130.16 (*ipso*-Ph), 150.68 (*ipso*-NO_2-Ph), 161.49 (C^2), 163.54 (C^4), 164.06 (C=O). ^{31}P NMR spectrum, δ_P, ppm: 15.2 (*Z*-isomer), 17.5 (*E*-isomer).

The organic solvents and reagents were purified by standard laboratory techniques. The ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded on Bruker WM-400 (^{1}H, 400 MHz) and Bruker AC-200 (^{13}C, 50.328 MHz; ^{31}P, 81.014 MHz) spectrometers in $CDCl_3$ relative to TMS (^{1}H, ^{13}C) and 85% phosphoric acid (^{31}P).

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