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Ethyl 2-(Diisopropoxyphosphoryl)-2H-azirine-3-carboxylate: Reactions with Nucleophilic 1,3-Dienes

M. José Alves,*a Américo Lemos,*b José Enrique Rodríguez-Borges,c Xerardo García-Mera,d A. Gil Fortesa

a Departamento de Química, Universidade do Minho, Campus de Gualtar, 4710-057 Braga, Portugal
Fax +351(253)678983; E-mail: mja@quimica.uminho.pt
b Departamento de Química, Bioquímica e Farmácia, Universidade do Algarve, Campus de Gambelas, 8005-137 Faro, Portugal
Fax +351(289)819403; E-mail: alemos@ualg.pt
c CIQ, Departamento de Química, Faculdade de Ciências, Universidade do Porto, Rua do Campo Alegre, 687, 4169-007 Porto, Portugal
d Departamento de Química Orgánica, Facultade de Farmacia, Universidade de Santiago de Compostela, 15782 Santiago de Compostela, Spain

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Abstract: Ethyl 2-(diisopropoxyphosphoryl)-2H-azirine-3-carboxylate, the first example of an azirine bearing simultaneously ester and phosphonate groups was generated in situ and reacted with a number of 1,3-dienes. Cycloadducts or their ensuing rearranged products were isolated in moderate yields.

Key words: 2H-azirines, aza-Diels–Alder cycloaddition, dienophiles, phosphonates

2H-Azirines have generated a great deal of interest due to their versatility as building blocks in the synthesis of important classes of heterocyclic compounds,1,2 and amino acids.3 2H-Azirines carrying ester groups are especially important not only due to their structural similarity to naturally occurring azirines with biological activity, like azirinomycin4 and (–)-(R)-dysdizirine antibiotics,5 but also for being excellent precursors in the synthesis of α- and β-amino acid derivatives. Azirines with C=O, P=O or heteroaromatic groups conjugated with the C=N bond, are effective dienophile partners6–10 in Diels–Alder cycloadditions, producing bicyclic and tricyclic compounds. 2H-Azirines devoid of electron-withdrawing groups only react with specially activated dienes such as 1,3-diphenylisobenzofuran in refluxing toluene11a,b or under Lewis acid catalysis.11c,d

Excitatory amino acids are the most common neurotransmitters in the mammalian central nervous system thus their receptors have been exploited in the treatment of several pathological conditions affecting the brain, such as Parkinson’s and Alzheimer’s diseases.12 (S)-2-Amino-3-phosphonopropanoic acid [(S)-AP-3, 1, Figure 1] is known to be a modulator for the N-methyl-d-aspartate (NMDA) receptor site.

In connection with our work on 2H-azirines, we envisaged that 2-(diisopropoxyphosphoryl)-2H-azirine-3-carboxylates would be excellent dienophiles for Diels–Alder cycloadditions, introducing simultaneously the biologically important phosphonate group13 into cycloadducts. This class of compounds has not been previously synthesized, despite of being closely related to (S)-AP-3 1.

This paper reports the unprecedented generation of ethyl 2-(diisopropoxyphosphoryl)-2H-azirine-3-carboxylate (5) and its interception by a number of electron-rich buta-1,3-dienes producing mono-, di-, and tricyclic aziridines, carrying the α-amino-β-phosphonate carbonyl moiety. The oxime 3 was obtained from ethyl bromopyruvate oxime (2)14 and triisopropyl phosphite. Its treatment with tosyl chloride in the presence of sodium carbonate led to β-phosphonic tosylxime ester 4 (Scheme 1). The corresponding 2H-azirine 5 was obtained under Neber conditions, but could not be isolated from the reaction medium. Although monofunctional 2H-azirine-2-phosphonates15

Figure 1 (S)-2-Amino-3-phosphonopropanoic acid

Scheme 1 Preparation of β-phosphonic tosylxime ester

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have been produced and isolated before under similar reaction conditions, manipulation of the reaction mixture in the present case, however, led to decomposition, according to $^1$H NMR analysis.

In a typical procedure tosyloxime $^4$ was solubilized in benzene mixed with potassium carbonate (10 equiv), triethylamine (0.3 equiv), and a 1,3-diene and stirred for four days at room temperature. The primary cycloadducts $^6$a,b,d,e were obtained in 9–59% yield. Derivative $^7$ was obtained in the case of reaction with the Danishefsky diene in 39% yield, by rearrangement of the primary cycloadduct $^6$c (Scheme 2). In case $^6$f, the silyl group cleaved during chromatography giving $^8$.

The moderate yields are certainly the reflection of the two-step sequence in the one-pot procedure together with the instability of the azirine because of the presence of the two electron-withdrawing substituents in the ring.

Cycloadduct $^6$a, obtained from reaction of azirine $^5$ with 2,3-dimethylbuta-1,3-diene, was isolated in very low yield, even in the presence of a large excess of diene (5 equiv). Difficulties of the same type had been reported by Davis in reaction of a $^2$H-azirine-3-phosphonate with 2,3-dimethylbuta-1,3-diene, where 100 equivalents of the diene were required. 9 Reaction of the azirine $^5$ with 1-methoxybuta-1,3-diene evidenced that the regioselectivity of the cycloaddition is governed by electronic effects. $^1$H and $^1$C NMR data of product $^6$b are in accordance with the electron-withdrawing effect of the two heteroatoms attached to C2; H2 is at $\delta_H = 4.80$ and C2 at $\delta_C = 85.6$. The cycloaddition products were obtained as single isomers, presumably formed by endo-selective processes, as generally observed in reactions of $^2$H-azirines with 1,3-dienes. 8 Furan and their derivatives are exceptions due to retro-Diels–Alder cycloadditions of the initially formed endo-cycloadduct that isomerize to the exo-products. 11b The low-field resonance of H3 in the tricyclic products obtained by reaction of $^2$H-azirines with cyclopentadiene is a clear feature of the endo selectivity. 8 This can be ascribed to the anisotropy of the backside double bond over H3, due to constraints of the tricyclic structure. The chemical shift value of H3 in compound $^6$d correspond to such an effect appearing at $\delta_H = 1.62$.

Features of pyridinone $^7$, obtained by rearrangement of $^6$c, are the two hydrogens of the CH$_2$ group, coupling to the phosphorus nucleus with $J = 12.0$ Hz; the signal at $\delta_H = 6.45$, assigned to H5, shows a doublet of doublets ($^3J = 3.0$ Hz to H3 and $^2J = 7.6$ Hz to H6) and two doublets at $\delta_H = 7.35$, corresponding to H6, and at $\delta_H = 7.03$, corresponding to H3, show matching couplings to H5. Rearrangements of this type have been noticed before in bicyclic adducts obtained from the Danishefsky diene and $^2$H-azirines bearing electrophilic groups. 16

In summary, cycloaddition reactions of ethyl 2-(diisoproxyphosphoryl)-$^2$H-azirine-3-carboxylate to nucleophilic dienes produced, in moderate yields, a number of functionalized six-membered-ring fused aziridines. These may eventually be valuable intermediates at the synthesis of interesting biological compounds related to (S)-AP3. Studies to improve the reaction efficiency as well as the

![Scheme 2](image-url)

Scheme 2  Generation of azirine $^5$ and its cycloaddition reactions with 1,3-dienes

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development of an asymmetric synthesis or generation of the azirine are ongoing. 

1H and 13C NMR spectra (100.6 or 75.5 MHz) were recorded on a Bruker Avance III 400 (400 MHz) spectrometer or on a Bruker WM AMX (300 MHz), using TMS as internal standard. IR spectra were recorded on a Perkin-Elmer 1640-FT spectrophotometer. Samples were run as thin films. Mass spectra were recorded on a VG Autospec M. Purification of crude samples was performed by dry flash chromatography, using silica gel purchased from Carlo Erba (35–70 μm).

Ethyl 3-(Diisopropoxyphosphoryl)-2-(hydroxyimino)propanoate (3)

To ethyl bromopropionate (4.5 g, 15 mmol) in CH2Cl2 (40 mL) was added P(Oi-Pr)3 (6 mL, 24 mmol) and the mixture stirred at 35 °C for 16 h. H2O (30 mL) was added and the mixture stirred at r.t. for a further 30 min and the organic phase was dried (MgSO4) and evaporated under vacuum. The oily residue was subjected to dry-flash chromatography (silica gel, CH2Cl2–EtOAc, polarity gradient or EtOAc–Hexanes, 10:1), affording 3 (5.13 g, 79%) as a colorless oil.

IR(neat): 3167, 2982, 2936, 1720, 1252, 995 cm–1.


Cycloaddition Reactions; General Procedure

To a soln of tosyloxime (4.5 g, 15 mmol) in benzene (5 mL) was added TsCl (3.24 g, 17 mmol) and the mixture stirred until the disappearance of the starting oxime (~4 h). The insolubles were removed by filtration and the solvent was evaporated to afford a residue that was subjected to dry-flash chromatography (silica gel, CH2Cl2–EtOAc, polarity gradient or EtOAc–Hexanes, 10:1), affording 3 (5.13 g, 79%) as a colorless oil.

IR(neat): 3167, 2982, 2936, 1720, 1252, 995 cm–1.


Ethyl 3-(Diisopropoxyphosphoryl)-2-azatricyclo[3.2.2.02,4]nonane (4)

To a soln of tosylamide (2.43 g, 10 mmol) in CH2Cl2 (40 mL) was added Na2CO3 (0.3 g, 0.69 mmol) in benzene (5 mL) was added TsCl (3.24 g, 17 mmol) and the mixture stirred until the disappearance of the starting oxime (~4 h). The insolubles were removed by filtration and the solvent was evaporated to afford a residue that was subjected to dry-flash chromatography (silica gel, CH2Cl2–EtOAc, polarity gradient or EtOAc–Hexanes, 10:1), affording 3 (5.13 g, 79%) as a colorless oil.

IR(neat): 3167, 2982, 2936, 1720, 1252, 995 cm–1.


Ethyl 7-(Diisopropoxyphosphoryl)-3,4-dimethyl-1-azabicyclo[3.2.2.02,4]nonane-6-carboxylate (6a)

Yield: 0.140 g (59%).

IR (neat): 3467, 2981, 2937, 1741 cm–1.

HRMS (FAB): m/z [M + H]+ calcd for C16H27NO5P: 344.1627; found: 344.1615.

Ethyl 7-(Diisopropoxyphosphoryl)-2-methoxy-1-azabicyclo[3.2.2.02,4]nonane-6-carboxylate (6b)

Yield: 0.125 g (51%).

IR (neat): 3467, 2981, 2937, 1741 cm–1.


Ethyl 3-(Diisopropoxyphosphoryl)-2-[tosyloxy]imino)propanoate (4)

To a soln of tosylamide (2.43 g, 10 mmol) in CH2Cl2 (40 mL) was added Na2CO3 (0.3 g, 0.69 mmol) in benzene (5 mL) was added TsCl (3.24 g, 17 mmol) and the mixture stirred until the disappearance of the starting oxime (~4 h). The insolubles were removed by filtration and the solvent was evaporated to afford a residue that was subjected to dry-flash chromatography (silica gel, CH2Cl2–EtOAc, polarity gradient or EtOAc–Hexanes, 10:1), affording 3 (5.13 g, 79%) as a colorless oil.

IR(neat): 3167, 2982, 2936, 1720, 1252, 995 cm–1.


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