Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 62 (2006) 1095–1101

Preparation and reactions of 3-phosphinyl-1-aza-1,3-butadienes. Synthesis of phosphorylated pyridine and pyrazole derivatives

Francisco Palacios,[a,*] Domitila Aparicio,[a] Yago López,[a] Jesús M. de los Santos[a] and José M. Ezpeleta[b]

[a]*Departamento de Química Orgánica I, Facultad de Farmacia, Universidad del País Vasco, Apartado 450, 01080 Vitoria, Spain*
[b]*Departamento de Física Aplicada II, Facultad de Farmacia, Universidad del País Vasco, Apartado 450, 01080 Vitoria, Spain*

Received 20 September 2005; revised 2 November 2005; accepted 2 November 2005

Available online 21 November 2005

Abstract—3-Phosphinyl 1-aza-1,3-butadienes **2** are obtained by aldol condensation between hydrazonoalkyl phosphine oxides and *N*,*N*-dimethylformamide dimethyl acetal. Transamination reaction of these azadienes with amines yields functionalized 1-aza-1,3-butadienes **3**. Cycloaddition processes of these azadienes **2a** with electron-poor dienophiles to give phosphorylated pyridine derivatives **9** and **15** are also reported, while intramolecular cyclization reaction of heterodiene **2b** affords phosphorylated pyrazole **17**.

1. Introduction

Hydrazones constitute an important class of compounds due to the rich chemistry of the hydrazono group and have attracted a great deal of attention in recent years because of their range of applications.[1] They have been extensively used as versatile precursors in acyclic[2] and heterocyclic synthesis,[3] and also form part of the structure of new azapeptides,[4] as well as biologically active compounds.[5]

Aza-Diels–Alder (ADA) reactions[6,7] of 1-azabutadienes are gaining widespread acceptance as tools in heterocyclic synthesis and have found use in the preparation of compounds containing pyridine, quinoline, mono- and diazaanthracene and other nitrogen rings. In particular, α,β-unsaturated dimethylhydrazones have been widely used in hetero Diels–Alder reactions, as 1-azadienes[8] (**I**, $R^1=NMe_2$) (Fig. 1) with electron-deficient partners, as key steps in a variety of syntheses of natural products and other biologically relevant heterocycles.[9]

In this context, we have been involved in the synthesis of 1-aza (**I**),[10] 2-aza-(**II**),[11] and 1,2-diaza-1,3-butadienes (**III**)[12] (Fig. 1) as well as new strategies for the preparation of nitrogen heterocyclic compounds.[13]

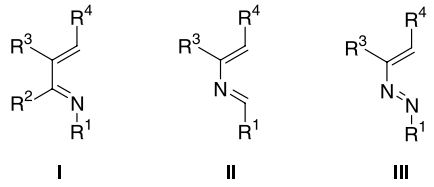


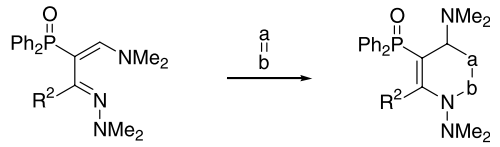
Figure 1.

However, as far as we know no examples of aza-Diels–Alder (ADA) reaction of 1-azadienes containing a phosphorus substituent at *C*-3 position (**I**, $R^1=NMe_2$, $R^3=P(O)Ph_2$, Fig. 1), have been reported. Furthermore, it is known that phosphorus substituents regulate important biological functions,[14] and that molecular modifications involving the introduction of organophosphorus functionalities in simple synthons could be very interesting for the preparation of biologically active compounds.

As a continuation of our work on the cycloaddition reaction of 1-azadienes and on the chemistry of new phosphorus- and nitrogen-substituted heterocycles, here we aim to explore the behaviour of 1-azadienes derived from dimethylhydrazones, such as 3-phosphinyl-1-aza-1,3-butadiene **Ia** (**I**, $R^1=R^4=NMe_2$, $R^3=P(O)Ph_2$) towards dienophiles (a=b), for the preparation of phosphorus-substituted heterocycles **IV** (Scheme 1), as well as the effect of subtituents at *C*-2 position of the azadiene. This strategy could open new entries for the preparation of substituted six-membered heterocycles.

Keywords: Hydrazones; 1-Aza-1, 3-buladienes; Phosphorylated heterocycles; Aza-Diels–Alder.
* Corresponding author. Tel.: +34 945 013103; fax: +34 945 013049; e-mail: francisco.palacios@ehu.es

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.11.003



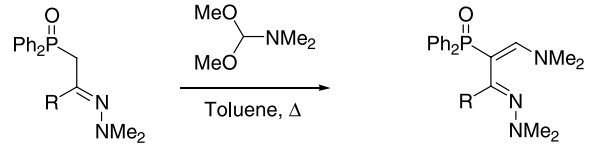
Ia **IV**

Scheme 1.

2. Results and discussion

2.1. Preparation of 3-phosphinyl 1-aza-1,3-butadienes 2

1-Aza-1,3-butadienes **2** (R=H, Me), containing electron-donating groups at *N*-1 and *C*-4 as well as an electron-withdrawing group at *C*-3 position, were prepared by aldol condensation between hydrazonoalkyl phosphine oxides **1** (R=H, Me) and *N*,*N*-dimethylformamide dimethyl acetal (Scheme 2). Thus, reaction of β-hydrazono phosphine oxide **1a** (R=H), prepared from methyl diphenylphosphine oxide, DMF and *N*,*N*-dimethylhydrazine (see Section 3), with *N*,*N*-dimethylformamide dimethyl acetal in refluxing toluene (TLC control) led to the formation of 1-azadiene **2a** (R=H) in good yield (Scheme 2). In the same way, 2-methyl-substituted 1-azadiene **2b** (R=Me) can be obtained by reaction of hydrazonoalkyl phosphine oxide **1b** (R=Me)[10b] with *N*,*N*-dimethylformamide dimethyl acetal. These compounds **2** were characterized by their spectroscopic data, and the vicinal coupling constant ($^3J_{PH}$) in the range of 15.0 Hz indicate a cis-relationship between the phosphorus atom and the vinylic proton, being consistent with an *E*-configuration for the carbon–carbon double bond.[15] ^{31}P NMR spectrum of **2a** showed one absorption at δ_P 33.1 ppm. Likewise, the ^{1}H NMR spectra of **2a** gave a well resolved doublet for the vinylic proton at δ_H 7.12 ppm ($^3J_{PH}$=15.0 Hz), while in ^{13}C NMR a doublet appeared at δ_C 146.0 ppm ($^2J_{PC}$=16.6 Hz) for the methine carbon.



1a R = H
1b R = Me

2a R = H
2b R = Me

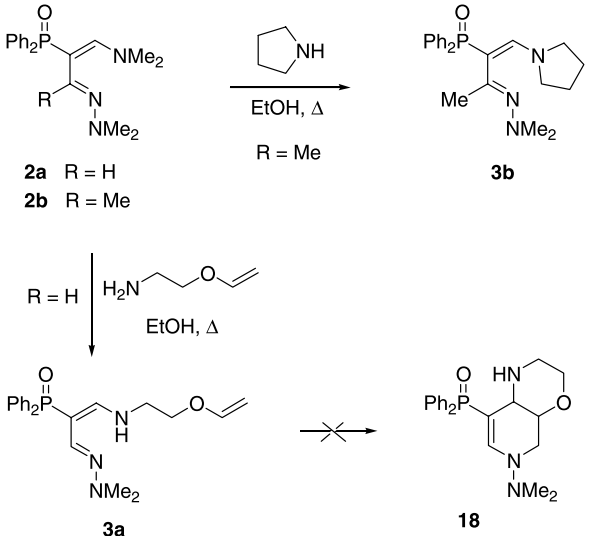
Scheme 2.

As far as we know, this process represents the first example for the preparation of 1-aza-1,3-butadienes containing a phosphorus electron-withdrawing group (Scheme 2).

These results prompted us to extend this reaction and to explore whether other phosphorylated 1-aza-1,3-butadienes can be obtained by transamination reaction of these 1-azadienes **2** with amine derivatives.

2.2. Transamination reaction of 4-dimethylamino 3-phosphinyl 1-aza-1,3-butadienes 2

We studied the transamination reaction between 1-azadienes **2** and simple and functionalized amines. Treatment of 1-azadiene **2b** (R=Me) with pyrrolidine in refluxing EtOH gave the transamination product **3b** in almost quantitative yield (Scheme 3). The spectroscopic data are in agreement with the assigned structure for compound **3b**. This process was extended to other functionalized amine derivatives. Thus, 2-vinyloxy ethylamine reacted with 1-azadiene **2a** (R=H) and gave, after purification, *N*-functionalized 1-aza-1,3-butadiene **3a** in 76% yield (Scheme 3).



2a R = H
2b R = Me

3b **3a** **18**

Scheme 3.

Next, we explore whether new phosphorylated 1-aza-1, 3-butadienes could be used as versatile tools for the construction of nitrogen-containing heterocycles through the cycloaddition reaction of these azadienes.

2.3. Cycloaddition reaction of 3-phosphinyl 1-aza-1,3-butadienes 2

The presence of electron-rich groups such as dimethylamino substituents on the terminal nitrogen atom (*N*-1) and on the terminal carbon atom (*C*-4) of the heterodiene system, may favour the Aza-Diels–Alder (ADA) cycloaddition of these substrates. In this way, 1-azadiene systems have been used as building blocks for the preparation of a wide range of heterocycles.[16] However, aza-Diels–Alder (ADA) reaction of 1-aza-1,3-butadienes **2** containing phosphorus substituents has not been reported, although, this strategy could be very useful for the preparation of phosphorylated azaheterocycles.[17]

Initially, we studied the cycloaddition reaction of electron-poor dienophiles such as tetracyanoethylene, naphthoquinone, diethyl azodicarboxylate, tosylisocyanate, diethyl fumarate, diethyl maleate, or maleic anhydride to azadiene **2a**. However, the formation of cyloadducts was not observed and decomposition products were obtained. In the same way, the addition of bromomaleic anhydride **4** or ethyl propiolate **5** to 1-azadiene **2a** gave the phosphorylated α,β-unsaturated nitrile **6** in moderate to good yield (Scheme 4). The formation of this nitrile **6** could be explained by transfer of the dimethylamino group of the azadienic system to the dienophile followed by oxidation to nitrile **6** as reported before for other authors.[18]