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First Synthetic and Theoretical Study of 1-aminovinylphosphonate esters as Substrates for the Diels-Alder Reaction

M. Mercedes Jiménez-Andreu,[a] Jorge Bueno-Morón,[a] Francisco J. Sayago,[a]* Carlos Cativiela,[a]* Tomás Tejero[a] and Pedro Merino[b]*

Dedication ((optional))

Abstract: The Diels-Alder reaction of 1-aminovinylphosphonate esters has been studied for the first time as a suitable procedure leading to quaternary carbocyclic α-aminophosphonates. The reaction is influenced by steric effects at the phosphonate functionality (bulky groups hinder the reaction) and electronic effects at the amino group (electron-withdrawing substituents increase the reaction rate). The *exo*/*endo* ratio is constant, and no influence of the solvent is observed. The experimental results have been rationalized by DFT methods.

Introduction

Among non-proteinogenic amino acids, quaternary α-amino acids constitute a family of compounds which find application in several research fields, from the development of new catalytic systems to the synthesis of pharmaceuticals.[1] Within this context, α,β-dehydroalanines are useful precursors of quaternary carbocyclic α-amino acids through cycloaddition reactions (Figure 1).[2]

α-Aminophosphonic acids are synthetic phosphorous analogues of α-aminoacids and their biological interest has been widely demonstrated.[3] However, although many efforts have been devoted to the synthesis of α,β-dehydroaminophosphonates[4] as synthetic intermediates of α-aminophosphonic acids,[5] their use as substrates for cycloaddition reactions has been scarcely explored. Only 1,3-dipolar cycloaddition reactions with diazoalkanes, mainly aimed at the synthesis of 1-aminocyclopropyl phosphonic acid derivatives, have been reported.[5c-e, 5h]

In this paper we present the first study of the use of α,β-dehydroaminophosphonates as suitable substrates in Diels-Alder reactions for the preparation of carbocyclic α-aminophosphonic acid derivatives (Figure 1). Cyclopentadiene was used as a model to assess the reactivity and selectivity of a variety of α,β-dehydroaminophosphonates bearing different protecting groups in the phosphonic acid and the amine functions. The reactivity and selectivity has been rationalized by DFT methods.

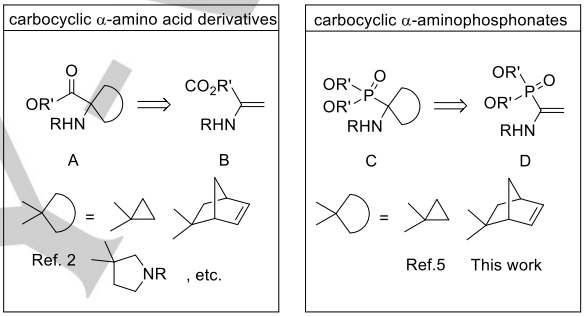

Figure 1. α,β-Dehydroalanines and 1-aminovinylphosphonate esters as substrates for cycloaddition reactions.

Results and Discussion

Firstly, the synthesis of a series of protected α,β-dehydroamino phosphonates was considered as suitable precursors of sterically hindered α-amino phosphonic acids (AAPA). A variety of carbamates (benzyloxycarbonyl and methoxycarbonyl groups) and amides (benzoyl, acetyl, trifluoroacetyl and *p*-nitrobenzoyl groups) were selected for this study. These groups will allow evaluating the influence of both steric and electronic effects in the course of the reaction as well as provide the opportunity of being deprotected if required in a further synthesis of AAPAs.

We envisioned the Horner-Wadsworth-Emmons (HWE) reaction as a suitable procedure to prepare the targeted 1-aminovinylphosphonate esters,[4],[6] since the starting α-aminomethyl-bisphosphonic acid, **1**, can be obtained in multi-gram scale.[7] Compound **1** was then acylated and subsequently esterified to afford *N*-protected tetraalkyl aminomethylbis-phosphonates **2a-f** in yields ranging from 20 to 90% (Scheme 1). The selected acylation procedure involves the use of triethylamine as base and treatment of the reaction crude with a strongly-acidic cation exchange resin. This methodology differs from the classical Schotten-Baumann procedure.[8] However, the high water-solubility of α-aminomethylbisphosphonic acid derivatives made us to discard these reaction conditions. The

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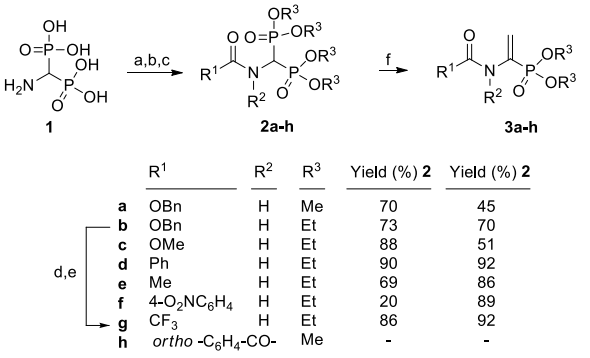
esterification reaction was carried out using trialkyl orthoformate derivatives as alkylating agents, which usually compare favourably with other procedures described in the literature.[9],[10]



	R^1	R^2	R^3	Yield (%) **2**	Yield (%) **2**
a	OBn	H	Me	70	45
b	OBn	H	Et	73	70
c	OMe	H	Et	88	51
d	Ph	H	Et	90	92
e	Me	H	Et	69	86
f	4-$O_2NC_6H_4$	H	Et	20	89
g	CF_3	H	Et	86	92
h	*ortho* -C_6H_4-CO-		Me	-	-

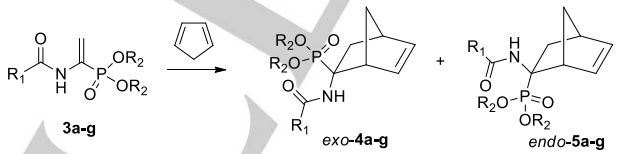
Scheme 1. Synthesis of dienophiles **3a-f**. Reagents and conditions: (a) H_2O/CH_3CN, Et_3N, R_1COX (CbzOSu for **2a** and **2b**, MeOCOOSu for **2c**, PhCOCl for **2d**, Ac_2O for **2e**, *p*-NO_2PhCOCl for **2f**, dimethyl terephthalate for **2h**), rt; (b) Dowex® 50WX8; (c) $HC(OMe)_3$ for **2a**, $HC(OEt)_3$ for **2b-f**, reflux; (d) H_2, 10% Pd/C, MeOH, rt; (e) TFAA, CH_2Cl_2, rt; (f) 37% HCHO(aq), Cs_2CO_3, THF/*i*PrOH (THF for compounds **3f** and **3g**), rt.

It should be noted that the *N*-trifluoroacetyl derivative 2g was obtained starting from the benzyloxycarbonyl derivative **2b** after hydrogenolysis, treatment with trifluoroacetic anhydride and olefination (Scheme 1), given that the acylation of aminomethylbisphosphonic acid, **1**, with trifluoroacetic anhydride failed. Finally, the *N*-protected α,β-dehydroamino-phosphonates **3a-g** were obtained by means of the HWE olefination with formaldehyde. Thus, α-aminomethylbis-phosphonates **2a-g** were treated with a 37% formaldehyde aqueous solution in the presence of cesium carbonate to afford the corresponding α-amino vinylphosphonates in good to high yields (45-92%).

In addition, the synthesis of the phthalimido derivative **3h** was also attempted. In our hands, the protection of tetraethyl aminomethylbisphosphonate with phthalic anhydride was unsuccessful and therefore, we addressed the synthesis of the tetramethyl derivative. Thus, hydrogenolysis of compound **2a** followed by treatment with phthalic anhydride provided a mixture of the tetramethyl phthalimido bisphosphonate, **2h**, and the partially protected amido acid derivative (a 39% conversion in the desired compound was observed in the NMR spectra of the reaction crude). However, the desired compound **2h** decomposed when the crude was submitted to column chromatography purification. Moreover, HWE olefination of the crude also led to a complex mixture. Presumably, these results can be explained by the high steric hindrance caused by the phosphonate groups.

The reaction of cyclopentadiene with 1-aminovinylphosphonate esters **3a-g** was then investigated. First attempts were conducted at room temperature under neat conditions or in the presence of Lewis acids ($AlCl_3$, $TiCl_4$ and $EtAlCl_2$). However, in these experiments no reaction was observed, or they led to decomposition, which discards the possibility of developing a catalytic process. After that, reactions were performed under neat conditions, without any additive, and the temperature was increased (Table 1). Thus, a mixture of an excess of cyclopentadiene and *N*-benzyloxycarbonyl derivative **3a** was stirred at 100°C for 7 days, at which time the Diels-Alder adducts *exo*-**4a** and *endo*-**5a** were isolated in 26% yield (entry 1). The ^{31}P NMR spectrum of the reaction crude showed the formation of various side-products along with the signals corresponding to the Diels-Alder adducts **4a** and **5a**. Under these reaction conditions, an 86:14 *exo*/*endo* ratio was observed (*exo* is referred to the phosphonate group).

Table 1. Diels-Alder reaction of *N*-acyl-1-aminovinylphosphonate esters **3a-g** with cyclopentadiene.



entry	substrate	R_1	R_2	solvent	T(°C)	time	Yield[a]	*exo*-**4**/*endo*-**5**[b]
1	**3a**	OBn	Me	neat	100	7 d	26%	86:14
2	**3a**	OBn	Me	neat	160	22 h	32%	86:14
3	**3b**	OBn	Et	neat	160	32 h	44%	86:14
4	**3c**	OMe	Et	neat	160	27 h	54%	88:12
5	**3d**	Ph	Et	neat	160	24 h	54%	84:16
6	**3e**	Me	Et	neat	160	18 h	51%	82:18
7	**3f**	4-$NO_2C_6H_4$	Et	neat	160	4 h	-	-
8	**3g**	CF_3	Et	neat	160	5 h	66%	86:14
9	**3f**	4-$NO_2C_6H_4$	Et	EtOH/water	75	17 d	45%	82:18
10	**3g**	CF_3	Et	EtOH/water	75	7 d	65%	84:16
11	**3g**	CF_3	Et	neat	150 (MW)	1 h	64%	85:15

[a] Isolated yield for both Diels-Alder adducts. [b] Determined by ^{31}P NMR of the crude reaction mixture.

The *exo*/*endo* ratio was determined by integration of the corresponding signals in the reaction crude ^{31}P NMR spectrum. The *exo*-/*endo*-stereochemistry of the isolated adducts was assigned by 2D-NOESY experiments and the analysis of characteristic vicinal $^{3}J_{P\text{-}C}$ coupling constants in the ^{13}C NMR spectra (see supporting information). At 160°C (entry 2) the cycloaddition with **3a** showed a complete conversion after 22 h, and the adducts **4a** and **5a** were isolated in a 32% yield. The *exo*/endo *ratio* remained unchanged and formation of side-products was diminished. After this result, we decided to perform the cycloaddition reactions with **3b-g** at 160°C.

Reaction of the diethyl dehydroaminophosphonate **3b** with cyclopentadiene was completed in 32 h. The ^{31}P NMR spectra of the crude showed less formation of side-products in comparison to that observed for compound **3a** (R_1 = Me), whereas the same *exo*/*endo* ratio was observed. Indeed, adducts *exo*-**4b** and *endo*-**5b** were obtained in a higher yield (44%, entry 3). This result prompted us to use diethyl phosphonate derivatives instead the corresponding dimethyl phoshonates. However, the longer reaction times required as a result of the higher steric hindrance of ethyl esters discourage the use of more voluminous substituents (^{i}Pr or Ph).

The effect of the nitrogen protecting groups was then evaluated. As showed in entries 2-6, shorter reaction times were needed for amide derivatives (benzoyl and acetyl, entries 5 and 6, respectively) in comparison with the corresponding carbamates (benzyloxycarbonyl and methoxycarbonyl, entries 3 and 4, respectively). The *exo*/*endo* ratios remained almost unchanged in all cases. Such small differences indicate that the steric hindrance of the protecting group at the amine function is not decisive in the reaction outcome so, it can be predicted that any carbamate including *tert*-butyl derivative might be used. It is worth noting that these results differ from those of the reaction of α,β-dehydroalanine derivatives with cyclopentadiene, where the observed *exo*/*endo* ratios depend on the nature and the steric hindrance of the *N*-acyl and ester groups. Moreover, they are generally lower than those observed for the corresponding 1-aminovinylphosphonate esters.[11],[12],[13]

Since differences in the steric hindrance or nature of the amine protecting groups did not led to a significant improvement of the reaction performance, we evaluated the influence of electronic effects (entries 7 and 8). Admittedly, the reaction between cyclopentadiene and compounds **3** is a typical normal demand Diels-Alder reaction; consequently, it should be expected that the presence of electron-withdrawing groups will tend to increase the reaction rate. Unfortunately, the reaction of cyclopentadiene with the *p*-nitrobenzoyl derivative **3f** resulted in decomposition. However, the reaction with the *N*-trifluoroacetyl dehydroaminophosphonate **3g** was completed in only 5 hours, affording the Diels-Alder adducts *exo*-**4g** *exo* and *endo*-**5g** in 66% combined yield and with a similar *exo/endo* ratio to those observed before. This result represents an improvement over the reactions with compounds **3a-e**, the best chemical yield was obtained in a shorter reaction time, and the *exo*-selectivity remained unaffected.

Once we found a sufficiently reactive substrate, we expanded the study of the reaction.

Firstly, the effect of the solvent was addressed. Although it is generally accepted that the solvent does not significantly affect the Diels-Alder reaction outcome as a result of a negligible difference in polarity between the initial state and the transition state,[14],[15] it is well known that both the reaction time and the stereoselectivity can be dramatically influenced by polar protic or aqueous media.[16] For instance, in the case of dehydroalanine derivatives, significant changes in stereoselectivity are observed when using ethanol[12] or water[17] as solvents. Consequently, the effect of a polar protic medium was investigated for compounds **3f** and **3g**, in ethanol-water as a solvent at 75°C (higher temperatures led to decomposition). Under these conditions, the *p*-nitrobenzoyl derivative **3f** did not lead to decomposition (presumably due to the lower temperature used), and the adducts *exo*-**4f** and *endo*-**5f** were obtained in 45% yield after 17 days of reaction (entry 9) at which time no more starting material was observed in the reaction mixture. An 82:18 *exo/endo* ratio was determined. The reaction with the *N*-trifluoroacetyl derivative **3g** was completed after 7 days, affording the adducts **4g** and **5g** in a 65% yield and 84:16 *exo/endo* ratio. These results confirm the limited effect exerted by including a polar solvent which, on the other side, favours decomposition at high temperatures, forcing the use of lower temperatures, which greatly increase the reaction time.

In addition, we investigated the effect of microwave irradiation on **3g** (entry 11). Thereby, a solution of the trifluoroacetyl derivative **3g** in cyclopentadiene was subjected to 100 W constant operating power (temperature was set to 150 ºC) for 1 hour, until consumption of the starting aminovinylphosphonate. Apart from the important improvement in the reaction time, no significant changes were observer in either the yield or the *exo*/*endo* ratio, which remained almost unchanged.

Furthermore, we also explored the synthesis of substituted aminovinylphosphonates. However, HWE reaction of **3g** with the more voluminous aldehyde ethanal failed. The NMR spectra of the reaction crude showed the attack of the amino group to the aldehyde to form a hemiaminal that reverts to the starting material when purification is attempted, thus illustrating the presence of an equilibrium rather the formation of the corresponding substituted alkene. Presumably, the higher steric hindrance of the aldehyde favours the attack of the nitrogen instead of that of acidic carbon.

The reversibility of the reaction was also investigated. To this end, a 66:33 mixture of *exo*-**4g** and *endo*-**5g** was stirred in cyclopentadiene at 160°C. After 5 h, the ^{1}H NMR spectra of the reaction mixture did not show any changes, concluding that the reaction was not reversible, and that thermodynamic control can be discarded for the observed selectivity. In this context the reaction was also investigated computationally by DFT methods to provide a rationale of the experimental results (for details see SI). Admittedly, the normal demand Diels-Alder reaction with phosphonates is less favored than the corresponding reactions with carboxylates because of the higher electron-withdrawing character of the latter when compared with the former, thus explaining the longer reaction times required for the described reactions in the present work. We located *exo* and *endo* transition structures for the reaction of cyclopentadiene with alkenes **AKb-g** equivalent to the corresponding alkenes **3b-g** (the only approximation used was replacement of Et by Me, i.e: R_2 = Me). In addition, alkenes **AKa,h,i** were also studied for the purpose of comparison (see below). We calculated the energy barriers for the reaction in gas phase and in ethanol as a solvent. The results are

collected in Figure 2. The observed values for energy barriers are in a good agreement with the experimental observations. The lower energy barrier corresponds to **AKg** (13.2 kcal/mol) corroborating the best result obtained with **3g**. Similarly, **AKf** showed also a low barrier (13.6 kcal/mol), whereas the more electron-rich alkene **AKi** exhibited a higher barrier (14.2 kcal/mol), as expected. Little influence was observed by moving from gas phase to ethanol as solvent, the former presenting lower barriers, in agreement with an apolar concerted reaction. In all cases, the *exo* adduct was predicted to be the preferred one although the differences with *endo* adducts predicted that the latter might be obtained as minor isomers. Finally, similar results were obtained for **AKe** (14.8 kcal/mol) and **AKh** (14.8 kcal/mol) demonstrating the absence of steric effects of the amino protecting group. The geometry of the transition structures evidenced differences between *endo* and *exo* approaches (see SI). Whereas the less favoured *endo* transition states showed to be clearly concerted, the preferred *exo* transition structures showed a marked asynchronicity, based on the different lengths of forming bonds.

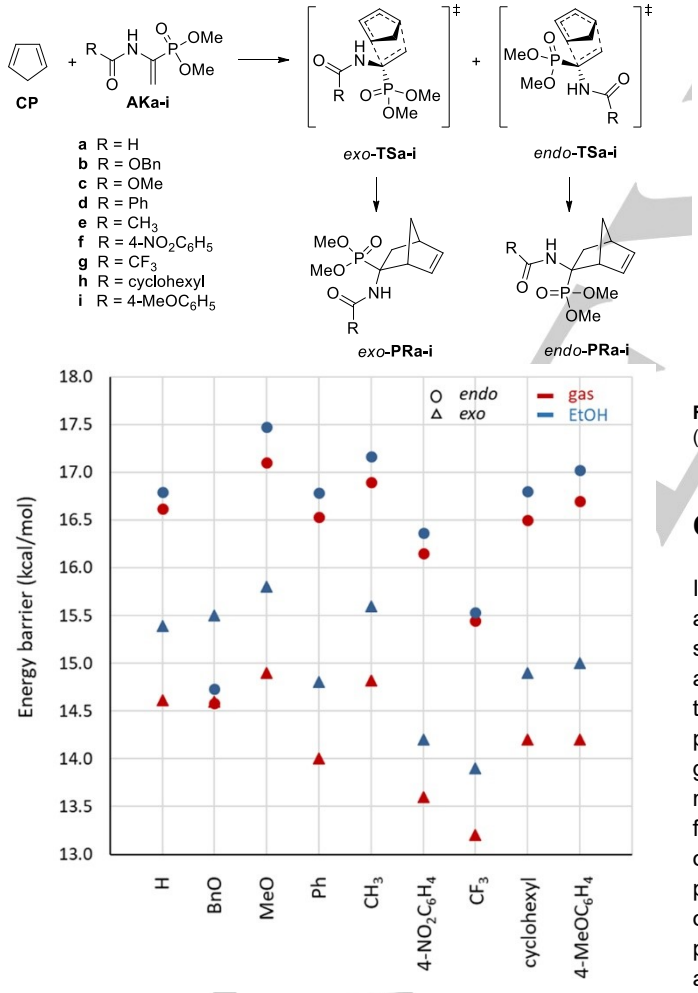


Figure 2. Energy barriers (b3lyp-d3bj/def2tzvp) for the reactions between cyclopentadiene and alkenes **AKa-i**.

Figure 3 illustrates both *endo*- and *exo*-**TSg** (the most favoured reaction) in which the asynchronicity is exemplified with distances of 1.97 and 2.65 Å for the C-C forming bonds in the most favored one (*exo*-**TSg**). A topological analysis of non-covalent interactions (NCI) confirmed H-F interactions that might also be responsible of the enhanced stability of *exo*-**TSg**. Such interactions are not observed in the case of *endo*-**TSg**.

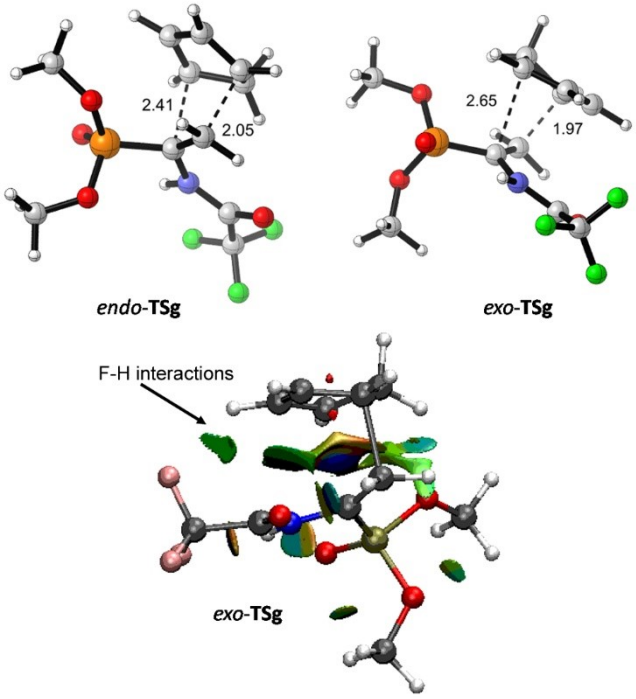


Figure 3. Optimized (b3lyp-d3bj/def2svp) geometries for *endo*- and *exo*-**TSg** (top) and NCI topological analysis of *exo*-**TSg** (bottom).

Conclusions

In conclusion, it has been demonstrated that 1-aminovinylphosphonate esters can be used as suitable substrates in Diels-Alder reactions leading to quaternary α-aminophosphonates. The reaction has some limitations, including the lack of reactivity or decomposition when conducted in the presence of a Lewis acids. Also, while the substituent at the amino group has no steric influence in the stereochemical course of the reaction, the presence of bulky substituents at the phosphonate function slowers the reaction. Since differences are already observed by moving from methyl to ethyl phosphonates, a cyclic phosphonate is not expected to show different results than those observed for Me or Et derivatives. These disappointing results prevent the use of chiral catalysts or auxiliaries to induce asymmetry, a subject that will require further investigations. On the other hand, the reaction takes place with good chemical yields in shorter reaction times by placing electron-withdrawing groups at the amino functionality. In particular, the trifluoroacetyl group, which can be easily removed, provided the best results. Moreover, the microwave-promoted reaction significantly shortened the

reaction time without loss of yield or stereoselectivity. Further research directed to introduce asymmetry in the reaction are ongoing and it will be communicated in due course.

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Keywords: Diels Alder reaction • Olefination • Phosphorous compounds • Density functional calculations • Strained molecules

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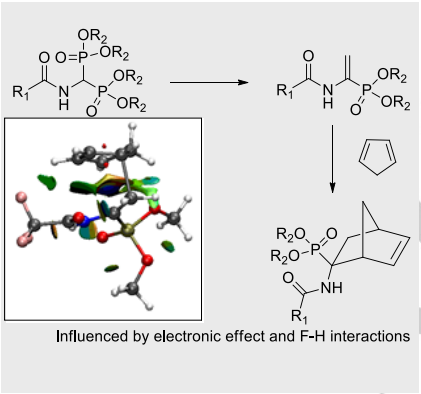

1-aminovinylphosphonate esters*

M. Mercedes Jiménez-Andreu, Jorge Bueno-Morón, Francisco J. Sayago, Carlos Cativiela* Tomás Tejero and Pedro Merino**

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