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Synthesis of new β- and γ-aminopyrrolidinephosphonates via 1,3-dipolar cycloaddition of substituted vinylphosphonates

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ABSTRACT

Synthesis of α- and β-(aminomethyl)vinylphosphonates was achieved from vinyl bromide via a cross-coupling reaction with triethyl phosphite and by cross-metathesis of allyl bromide and vinylphosphonate, respectively. The 1,3-dipolar cycloaddition of these vinylphosphonates with a dipole in the presence of trifluoroacetic acid afforded selectively the β-aminopyrrolidinephosphonates. Syntheses of *cis*- and *trans*-γ-aminopyrrolidinephosphonates are also described.

1. Introduction

Vinylphosphonates have been known for several decades[1] and constitute a very important class of building blocks for the synthesis of complex structures,[2] including biologically active molecules.[3] The β-aminovinylphosphonates, although rarely described,[4] have been used for the synthesis of β-aminophosphonic acid derivatives[5] that display interesting biological properties such as antibiotics,[6] enzyme inhibitors,[7]and anti-HIV agents.[8] However, synthesis of heterocyclic β-aminophosphonates, in particular pyrrolidine analogues, remains a challenge.

Syntheses of substituted pyrrolidines are largely reported by cycloaddition of a 1,3-dipole with vinyl derivatives.[9] To the best of our knowledge, only one 1,3-dipolar cycloaddition reaction has been reported between a 1,3-dipole and an unsubstituted vinylphosphonate to provide a heterocyclopentylphosphonate.[10] On the contrary, the 1,3-dipolar cycloaddition reaction with substituted vinylphosphonate is still unknown.

In continuation of our work on the development of new methodology for the synthesis of heterocyclic aminophosphonic acids,[11] and considering the importance of heterocyclic aminophosphonates in synthetic, agrochemical, and medicinal chemistry,[12] we decided to investigate the 1,3-dipolar cycloaddition of α- and β-substituted vinylphosphonates with azomethine ylides to access a range of pyrrolidines, for phosphonopeptide construction (Fig. 1).

In this Letter, we report the synthesis of the first members of a new class of β- and γ-aminophosphoryl pyrrolidines.

2. Results and discussion

Synthesis of β-aminovinylphosphonates **1** was achieved by the S_N2 displacement of the allylic bromide **2** by oxazolidinone or amide **3** in the presence of a base (Cs_2CO_3 or NaH). Then, vinyl bromide **4** was coupled with triethyl phosphite at 150 °C in the presence of a catalytic amount of nickel bromide.[13] The resulting vinylphosphonates **1** were obtained in good yields (Scheme 1, Table 1).[14]

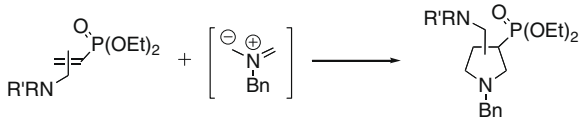
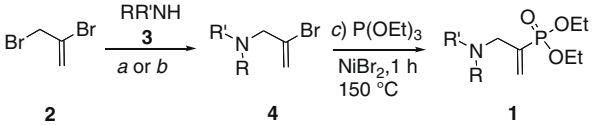


Figure 1. β- and γ-Aminopyrrolidinephosphonates.



Scheme 1. Synthesis of β-aminovinylphosphonates: see Table 1.

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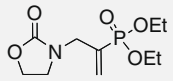
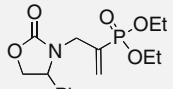
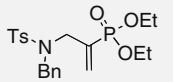
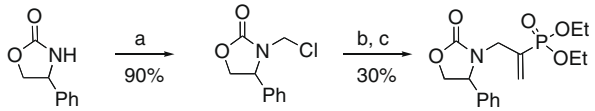
Table 1
Formation of vinylphosphonates **1a–c** produced via Scheme 1

Entry	R-NH-R′ **3**	**4** (Yield %)	**1**[c] (Yield %)	Vinylphosphonate **1a–c**
1	 **3a**	**4a** (78)[a]	**1a** (74)	
2	 **(±)-3b**	**4b** (61)[a]	(±)-**1b** (89)	
4	 **3c**	**4c** (76)[b]	**1c** (82)	

[a] Reaction conditions: NaH, DMF, rt, 12 h.
[b] Cs_2CO_3, CH_3CN, reflux, 2 h.
[c] Solvent-free reaction of **4** with $P(OEt)_3$ 5 equiv, $NiBr_2$ 20 mol %, 150 °C, 1 h.



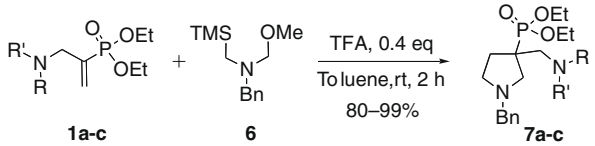
Scheme 2. Reagents and conditions: (a) $(CH_2O)_n$, TMSCl excess, reflux, 2 h; (b) NaH, $CH_2[P(O)(OEt)_2]_2$, THF, 0 °C; (c) NaH, $(CH_2O)_n$ 5 equiv, THF, rt.

It is noteworthy that the preparation of **1b** from oxazolidinone (±)-**3b** by chloromethylation [$(CH_2O)_n$/TMSCl] to afford oxazolidinone **5**, and subsequent alkylation [$CH_2(P(O)(OEt)_2)_2$] and vinylation [NaH/$(CH_2O)_n$][4d] gave only a poor yield of the vinylphosphonate (±)-**1b** (Scheme 2).

For this study, the 1,3-dipole derived from **6** (an expensive commercial product) was prepared from benzylamine by following a well-known procedure.[9] With vinylphosphonates **1a–c** in hand, we submitted them to a 1,3-dipolar cycloaddition with amine **6** in the presence of trifluoroacetic acid (TFA) in toluene at room temperature (Scheme 3). Under these conditions the desired β-aminophosphonates **7a–c** were produced in excellent yields (Table 2).[15]

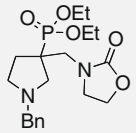
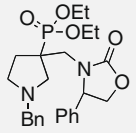
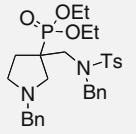
In order to expand the scope of our method, we decided to prepare the heterocyclic aminophosphonates via the cycloaddition of dipole derived from **6** with the *cis*- and *trans*-γ-aminophosphonates **9c** and **12c**, respectively. The preparation of *cis*-vinylphosphonate **9c** was achieved by alkylation of *N*-tosyl amine **6c** followed by phosphorylation to provide aminoalkynephosphonate **8c**. Subsequent Lindlar hydrogenation (5 wt % Pd on $CaCO_3$) of the latter afforded the *cis*-γ-aminophosphonate **9c** in good yield.[16]

trans-Aminovinylphosphonate **12c** was prepared selectively by cross-metathesis of allyl amide **10** and vinylphosphonate **11** using Grubbs II catalyst (5 mol %)[17] in dichloromethane at reflux for 20 h (Scheme 4).[18] Assignment of the stereochemistry of **9c** and **12c** was confirmed by the analysis of ^3J coupling constants between H-3 and the phosphorus atom. The observed values ($^3J_{PHtrans}$ = 51.7 Hz)

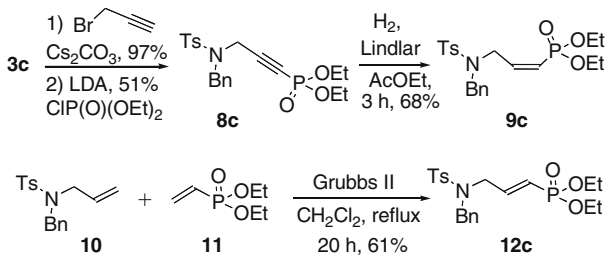


Scheme 3. β-Aminophosphonates by 1,3-dipolar cycloaddition.

Table 2
Formation of β-aminophosphonates **7a–c** produced via Scheme 3

Entry	R-NH-R′ **1**	**7** (Yield %)	β-Aminophosphonates **7a–c**
1	**1a**	**7a** (80)	
2	(±)-**1b**	(±)-**7b** (99)[a]	
4	**1c**	**7c** (91)	

[a] Diastereoisomeric excess de = 8%.

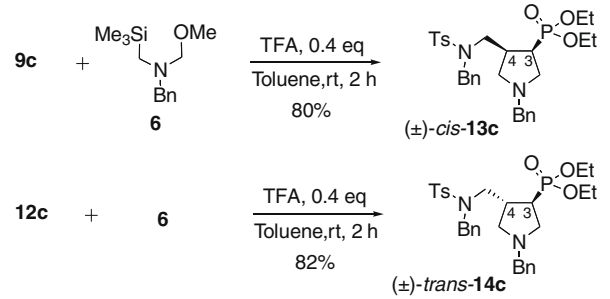


Scheme 4. Synthesis of γ-aminovinylphosphonates.

for **9c** and ($^3J_{PHcis}$ = 22.0 Hz) for **12c** are in agreement with the literature.[4c,d]

The 1,3-dipolar cycloaddition of *cis*- and *trans*-aminovinylphosphonates **9c** and **12c** was achieved under the same conditions as noted above. Amine **6** and aminovinylphosphonates **9c** and **12c** were treated with TFA in toluene at room temperature to produce, with complete stereoselectivity, the heterocyclic γ-aminophosphonates *cis*-**13c** and *trans*-**14c** in good yields (Scheme 5).[19] The relative stereochemistry of *cis*-**13c** and *trans*-**14c** was supported by coupling constants in ^{13}C NMR spectra between P and CH_2–C-4. The observed values ($^3J_{PCcis}$ = 7.2 Hz) for **13c** and ($^3J_{PCtrans}$ = 0 Hz) for **14c** were in agreement with our reported data in a related system.[20]

Selective deprotection of *N*,*N*-dibenzylaminophosphonate **7c** by hydrogenolysis with a catalytic amount of 20% $Pd(OH)_2$/C in AcOH/HCl under hydrogen (1 atm, 20 h), gave aminophosphonate **15c**[21] in good yield (Scheme 6).[22]



Scheme 5. Synthesis of *cis*- and *trans*-γ-aminophosphonates.