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Synthesis of Azaheterocyclic Vinylphosphonates by Ring-Closing Metathesis

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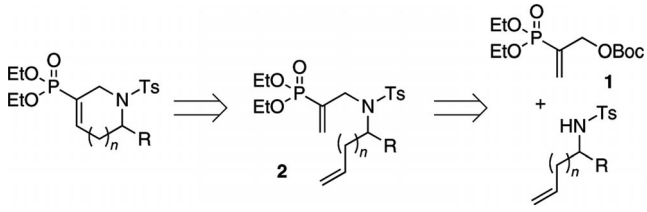
The title compounds were synthesized by ruthenium-catalyzed ring-closing metathesis of *N*-tosyl-*N*-(ω-alkenyl)-aminomethylvinyl phosphonates, which were obtained from *N*-(ω-alkenyl)-*N*-tosylamides. These compounds, in turn, were prepared from unsaturated alcohols through the Mitsunobu reaction. This methodology gives access to five- and six-membered ring compounds. Additionally, chiral phosphonates can be obtained easily.

Introduction

Aminophosphonic acids and their derivatives constitute an important class of biologically active molecules.[1] Although less studied, β-aminovinylphosphonates have received attention as a result of their use in the preparation of β-aminophosphonic acids derivatives, which display interesting biological properties,[2] and because of their use in the synthesis of 2,4-disubstituted tetrahydrothiophenes.[3] Whereas several synthetic methods for acyclic β-aminovinylphosphonates have been reported,[4] only a few reports on the preparation of their cyclic counterparts exist, that is, by palladium-catalyzed Hirao coupling[5] or through organocatalyzed annulations of allenic phosphonates.[6] We became interested in the synthesis of this class of compounds, as some of them are reported to possess antiantagonist activity at GABA (γ-aminobutyric acid) receptors,[7] or may lead to phosphodiesterase inhibitors.[5] It occurred to us that these cyclic phosphonates, namely, azaheterocyclic vinylphosphonates, would result from the ring-closing metathesis (RCM) of suitably protected (aminomethyl)vinylphosphonates **2**. These compounds, in turn, could be obtained through the organocatalyzed substitution reaction of diethyl α-(*tert*-butoxycarbonyloxymethyl)vinylphosphonate (**1**)[8] by a *N*-*p*-toluenesulfonamide possessing a terminal double bond, namely, *N*-(ω-alkenyl)-*p*-toluenesulfonamide (Scheme 1).



Scheme 1. Retrosynthetic approach to azaheterocyclic vinylphosphonates.

Results and Discussion

However, the planned approach may be hampered by the synthesis of such *N*-*p*-toluenesulfonamides, as the methods available for their preparation are limited to direct tosylation of alkenylamines[9] or alkylation of *p*-toluenesulfonamide by ω-bromoalkenes.[10] These two methods cannot be generalized because of the low availability of the starting materials. Therefore, we turned towards the use of the Mitsunobu reaction. By starting with the work of Weinreb[11] and Dobbs,[12] we devised the synthesis of several *N*-Boc,*N*-(ω-alkenyl)-*p*-toluenesulfonamides by reaction of *N*-Boc-*p*-toluenesulfonamide with ω-alkenyl alcohols.

After some experimentation, it appeared that the usual Mitsunobu conditions, that is, diethyl azodicarboxylate (DEAD)/triphenylphosphane (PPh_3) in THF at room temperature gave miscellaneous results, with formation of by-products, whereas the use of DEAD/1,2-bis(diphenylphosphanyl)ethane (dppe) in THF at room temperature led to much better yields. Thus, we could easily obtain several allylic and homoallylic *N*-Boc,*N*-(ω-alkenyl)-*p*-toluenesulfonamides (Table 1), which afforded the required *N*-(ω-alkenyl)-*p*-toluenesulfonamides upon subsequent cleavage of the Boc group with trifluoroacetic acid in dichloromethane at room temperature. It is noteworthy that chiral alcohols reacted without any racemization (Table 1, entries 2 and 4).

With those reagents in hand together with those already described,[11,12] the synthesis of the required phosphonates for the final RCM step was straightforward with the use of our recently reported[8] 1,4-diazabicyclo[2.2.2]octane (DABCO)-catalyzed substitution from **1**. Thus, the reac-

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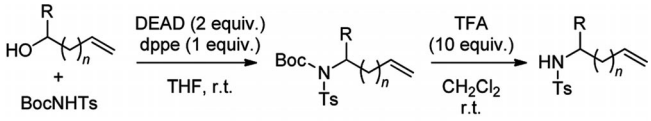
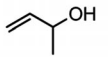
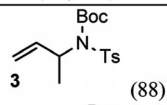
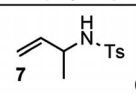
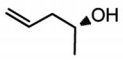
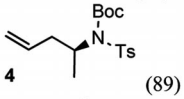
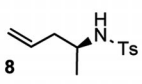
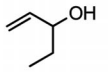
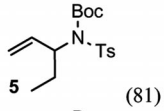
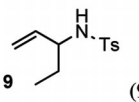
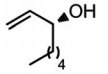
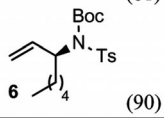
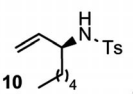
Table 1. Synthesis of *N*-(ω-alkenyl)-*p*-toluenesulfonamides **7**–**10** by Mitsunobu reaction.[a]



Entry	Starting alcohol	*N*-Boc-tosylamide (% yield) [a]	Tosylamide (% yield) [a]
1		 **3** (88)	 **7** (98)
2		 **4** (89)	 **8** (97)
3		 **5** (81)	 **9** (93)
4		 **6** (90)	 **10** (97)

[a] Isolated yields are given.

tions were carried out in THF at room temperature and were usually complete after 1 h; the yields ranged from 77 to 98% (Table 2).

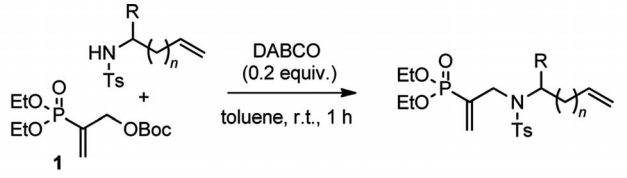
Finally, the RCM step was carried out by using these phosphonates. A great number of catalysts have been reported for the metathesis reaction,[13] and ruthenium carbene complexes are the most widely used, particularly for the synthesis of organophosphorus compounds.[14] We rapidly found that the first-generation Grubbs catalyst (**A**, Figure 1) was ineffective in our case, which is not a surprising result, as the starting vinylphosphonates belong to the class III olefins, which are known to react with difficulty.[15] Therefore, we used more-active catalysts such as the second-generation Grubbs catalysts (**B**) and the Hoveyda–Grubbs catalysts (**C**), which were much more satisfactory.

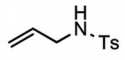
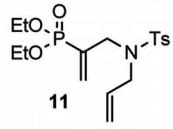
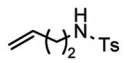
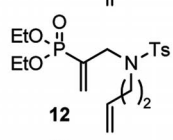
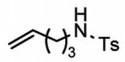
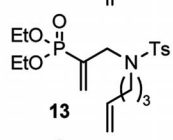
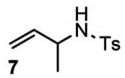
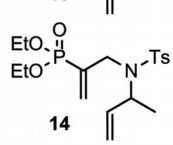
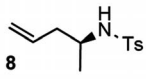
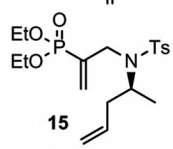
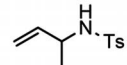
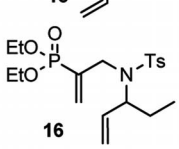
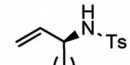
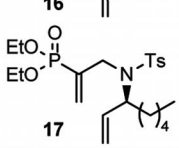
Thus, a series of five-membered azaheterocyclic phosphonates (Table 3) could be easily obtained under rather dilute conditions (substrate: 0.02 M) with low catalyst loading (5 mol-%) by using either **B** or **C**; both catalysts gave essentially similar results. Also, chiral phosphonates were obtained from enantiomerically pure *p*-toluenesulfonamides without any racemization, as checked by careful chiral HPLC analysis. Thus, the presence of an alkyl substituent α to the nitrogen atom did not affect the yield.

From an experimental point of view, the products were contaminated with black ruthenium byproducts that could not be removed by flash chromatography. However, treatment of the crude product with activated charcoal prior to chromatography, as already described,[16] allowed clean and efficient removal of these impurities.

The synthesis of the six-membered ring analogues is outlined in Table 4. Azaheterocyclic phosphonate **22** was obtained efficiently by using both catalysts, but this time the Grubbs II catalyst (**B**) gave the highest yield (Table 4, entry 1 vs. 2). In contrast to five-membered ring phosphonates, the presence of a methyl substituent α to the nitrogen atom (Table 4, entries 3 and 4) led to a mixture of three compounds (i.e., **19**, **23**, and **24**), in which expected azaheterocyclic phosphonate **23** was formed in low amounts

Table 2. Synthesis of *N*-tosyl-*N*-(ω-alkenyl)aminomethylvinyl phosphonates.[a]



Entry	Tosylamide	Product	Yield[b] [%]
1		 **11**	90
2		 **12**	98
3		 **13**	94
4	 **7**	 **14**	86
5	 **8**	 **15**	80
6	 **9**	 **16**	79
7	 **10**	 **17**	79

[a] Reactions conditions: **1** (1 mmol), *N*-(ω-alkenyl)-*p*-toluenesulfonamide (1.1 mmol), and DABCO (0.2 mmol) were stirred in anhydrous toluene (5 mL) at room temperature for 1 h. [b] Isolated yield.

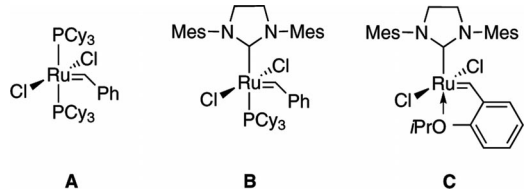
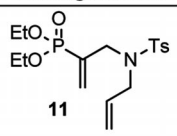
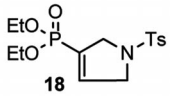
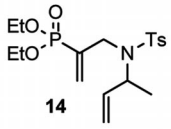
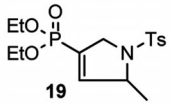
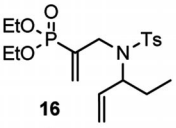
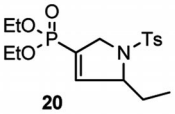
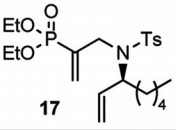
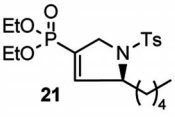


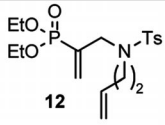
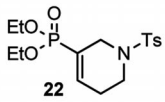
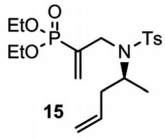
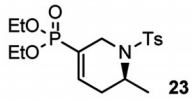
Figure 1. Catalysts used for the RCM reaction of *N*-tosyl-*N*-(ω-alkenyl)aminomethylvinyl phosphonates.

Table 3. Synthesis of five-membered ring azaheterocyclic vinylphosphonates by RCM.[a]

Entry	Starting material	Product	Cat.	Yield[b] [%]
1	 **11**	 **18**	**B**	quant.
2	**11**	**18**	**C**	94
3	 **14**	 **19**	**B**	62
	14	**19**	**C**	94
5	 **16**	 **20**	**C**	96
6	 **17**	 **21**	**C**	87

[a] Reactions were carried out with the catalyst (5 mol-%) in refluxing dichloromethane for 24 h. [b] Isolated yield.

Table 4. Synthesis of six-membered ring azaheterocyclic vinylphosphonates by RCM.[a]

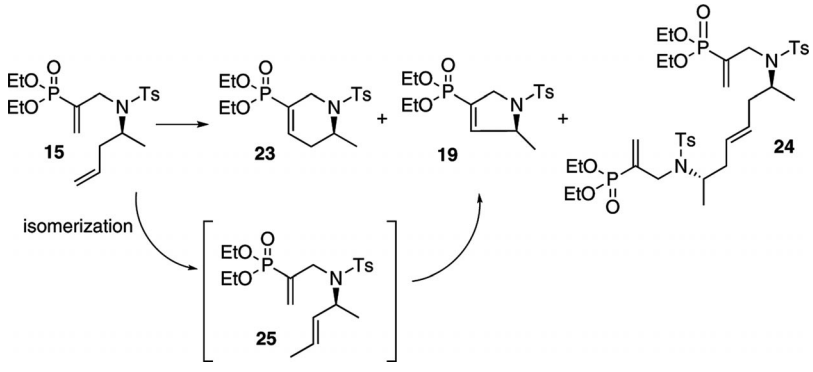
Entry	Substrate	Product(s)	Cat.	Yield[b] [%]
1	 **12**	 **22**	**B**	quant.
2	**12**	**22**	**C**	80
3	 **15**	**19**  **23** **24**	**B**	9 23 60
4	**15**	**19** **23** **24**	**C**	9 24 62
5	**15**	**23** **24**	**C**	31 63[c]
6	**15**	**23** **24**	**C**	20 75[d]

[a] Reactions were carried out with the catalyst (5 mol-%) in refluxing dichloromethane for 24 h. [b] Isolated yield. [c] With 1,4-benzoquinone (10 mol-%). [d] With titanium isopropoxide (30 mol-%).

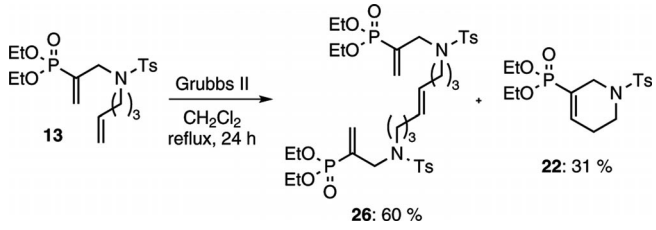
(23–24% yield), regardless of the catalyst. Byproduct **24** was formed from competitive homodimerization of the substrate, and **19** resulted from RCM of **25**, which was formed by migration of the double bond in **15** prior to cyclisation (Scheme 2).

This side reaction was reported several times, and different additives were used for its suppression.[17] Accordingly, we carried out the RCM reaction of **15** in the presence of 1,4-benzoquinone (10 mol-%), which resulted in complete elimination of side product **19** (Table 4, entry 5). The same result was obtained in the presence of titanium isopropoxide (30 mol-%; Table 4, entry 6), but the amount of homodimerization product **24**[18] remained identical in both reactions. This high amount of homodimerization product reflects the fact that, although the vinylphosphonate moiety is reactive towards the RCM reaction (as exemplified in the five-membered ring series), the entropic factor that accounts for cyclization is less pronounced in this case. The use of catalyst **B** instead of **C** gave essentially the same results.

Finally, we were interested in using substrate **13** to afford a seven-membered ring azaheterocyclic vinylphosphonate, which has never been formed. Instead, only products **26** (arising from homodimerization) and **22** (formed by RCM of the isomerized substrate) were obtained in 60 and 31% yield, respectively, regardless of the catalyst and the conditions employed (Scheme 3). The presence of benzoquinone or titanium isopropoxide did not improve the reaction outcome.



Scheme 2. Different products obtained from metathesis of **15**.



Scheme 3. Different products obtained from metathesis of **13**.

Conclusions

In summary, we have described the synthesis of azaheterocyclic vinylphosphonates through the RCM reaction of *N*-tosyl-*N*-(ω-alkenyl)aminomethylvinylphosphonates, which are easily obtained by DABCO-catalyzed substitution of diethyl α-(*tert*-butoxycarbonylmethyl)vinylphosphonate (**1**) by *N*-(ω-alkenyl)-*N*-tosylamides. Whereas five-membered ring azaheterocyclic vinylphosphonates were easily obtained in good yields, their six-membered counterparts gave less satisfactory results, as side reactions such as homodimerization and double-bond isomerization of the substrate occurred to a large extent. Although the latter reaction could be suppressed by the presence of additives in the RCM reaction, homodimerization remains a competitive side reaction. Nevertheless, the separation of this homodimerization byproduct from the desired compound by flash chromatography was a rapid and efficient task, and as such, the reaction remains synthetically useful. Finally, additional appeal of this methodology lies in the fact that chiral compounds may be obtained easily.

Experimental Section

Synthesis of ω-Alkenyl-*N*-(*tert*-butoxycarbonyl)-*p*-toluenesulfonamides: DEAD (232 μL, 1.48 mmol, 2 equiv.) was added dropwise to a cooled (0 °C) and stirred solution of *p*-toluenesulfonamide (200 mg, 0.74 mmol, 1 equiv.), dppe (294 mg, 0.74 mmol, 1 equiv.), and the alcohol (0.81 mmol, 1.1 equiv.) in dry THF (7 mL) under an atmosphere of argon. The mixture was then stirred at room temperature. After complete consumption of the reagent, the mixture was filtered through Celite. The solvent was removed in vacuo, and the residue was purified by flash chromatography on silica gel.

Synthesis of ω-Alkenyl-*p*-toluenesulfonamides: Trifluoroacetic acid (0.41 mL, 5.54 mmol, 10 equiv.) was added dropwise to a stirred solution of protected *p*-toluenesulfonamide (0.55 mmol, 1 equiv.) in dichloromethane (9 mL). The mixture was then stirred at room temperature for 24 h. After complete consumption of the reagent, aqueous 10% $NaHCO_3$ was added slowly until a basic pH was reached. NaCl was then added, before extraction with dichloromethane. The organic layer was washed with brine and dried with $MgSO_4$. After filtration and removal of the solvent in vacuo, the residue was purified by flash chromatography on silica gel.

Synthesis of Diethyl *N*-Tosyl-*N*-(ω-alkenyl)aminomethylvinyl Phosphonates: A solution of ω-alkenyl-*p*-toluenesulfonamide (1.05 equiv.) in toluene (2 mL) and DABCO (22.5 mg, 0.2 mmol, 0.2 equiv.) were added to a solution of diethyl α-(*tert*-butoxycarbonyloxymethyl)vinylphosphonate (**1**; 294 mg, 1 mmol) in anhydrous toluene (3 mL) under an atmosphere of argon. The mixture was stirred at room temperature for 1 h. The solvent was removed in vacuo, and the residue was purified by flash chromatography on silica gel.

Synthesis of Diethyl Azaheterocyclic Vinylphosphonates by RCM: A solution of *N*-tosyl-*N*-(ω-alkenyl)aminomethylvinyl phosphonate (0.26 mmol, 1 equiv.) in dichloromethane (10 mL) was added to a solution of catalyst **B** or **C** (0.013 mmol, 0.05 equiv.) in anhydrous and degassed dichloromethane (3 mL) under an atmosphere of argon. The mixture was heated at reflux for 24 h, with TLC monitoring. After total consumption of the reagent, the solvent was removed in vacuo. The residue was dissolved in ethyl acetate (10 mL) and charcoal (1 g) was added. The suspension was stirred at room temperature for 48 h and filtered. Ethyl acetate was removed in vacuo, and the residue was purified by flash chromatography.

Supporting Information (see footnote on the first page of this article): ^1H NMR and ^{13}C NMR assignments and copies of the ^1H NMR, ^{13}C NMR, and ^{31}P NMR spectra.

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[18] Although analysis of **24** by NMR spectroscopy was not conclusive about the stereochemistry of the double bond, it is reasonably considered as the *E* isomer.

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