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Cerium(IV) Ammonium Nitrate Mediated 5-*endo*-dig Cyclization of α-Amino Allenylphosphonates to Spirodienones

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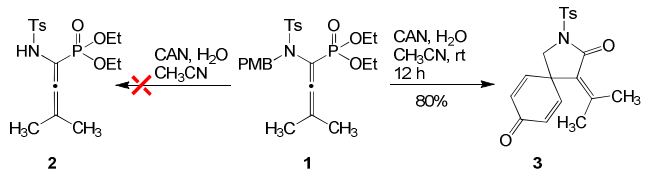
α-Amino allenylphosphonates were treated with cerium(IV) ammonium nitrate in various conditions to form spirodienones in good to excellent yields. This 5-*endo*-dig cyclization proceeds through the formation of a key iminium intermediate. A comprehensive study on the nature of the solvent used for this reaction was undertaken resulting in the formation of three types of spirodienone scaffold.

A large number of complex molecules with interesting biological activities present a spirocyclic core. In the recent years a growing interest in building such core has led to numerous reports on the synthesis of spirocyclic derivatives such as spiroacetals,[1] spirolactams,[2–7] spirolactones,[8] spirooxindoles,[9,10] spiroindolones,[11] and spirocyclanes[12] just to name a few. Spirocyclohexadienones are an important class of precursors for the construction of such complex structures.[13–16] Moreover, the spirocyclohexadienone motif could be found in natural products. For instance, in 2004, Wu and co-workers isolated the annosqualine, an spirodienone lactam, from the stems of *Annona Squamosa* L.[17] The classical methods of formation of azaspirodienones involve dearomative spirocyclization using hypervalent iodine reagents and phenol derivatives,[18–24] radical cyclization,[25,26] Ru complex-mediated dearomatization.[27,28]

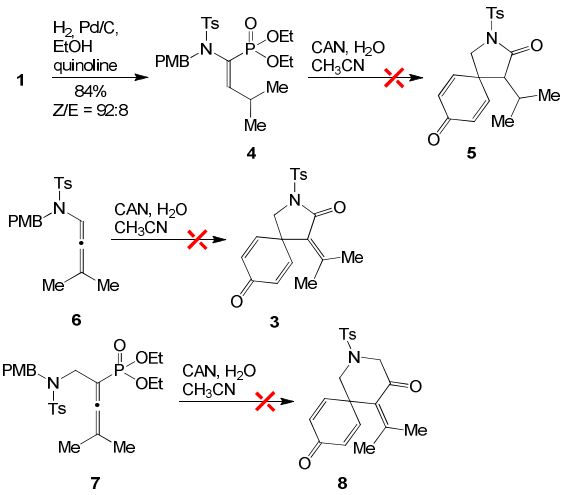
In the course of our recent work on the synthesis of α-amino vinylphosphonates[29,30] through the reduction of α-amino allenylphosphonates,[31] such as **1**, we were interested to prepare *para*-methoxybenzyl protected allenylphosphonates to easily deprotect them as free α-amino allenylphosphonates **2** (Scheme 1). Cerium ammonium nitrate (CAN) is a well-known reagent to deprotect *N*-sulfonyl *N*-*para*-methoxybenzyl compounds.[32] However, in the case of the α-amino allenylphosphonate **1** no deprotection product **2** was observed, instead the spirodienone lactam **3** was obtained in 80% yield (Scheme 1). The structure of the spirodienone lactam **3** was determined by ^{1}H and ^{13}C NMR analysis and compared to similar structures presented in the literature.[28,33]



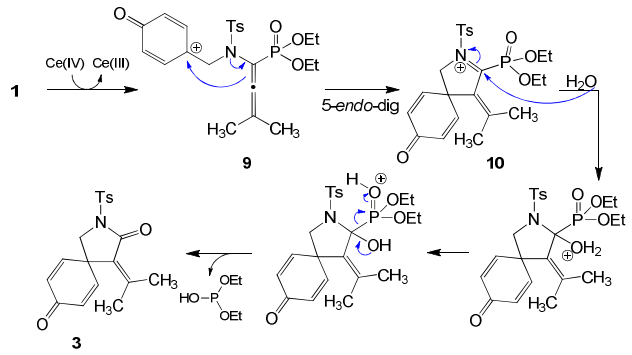
Scheme 1. 5-*endo*-dig cyclization of α-amino allenylphosphonates

To determine the mechanism of this cyclization we investigated the influence of all the substituents present on the starting material for the formation of the spirodienone lactam **3**. The reduction of the allene moiety led to the alkene **4**[29] which was treated with CAN to prepare the spirodienone lactam **5**. The lack of reactivity of this substrate **4** led to the conclusion that the digonal carbon on the allene moiety was involved in the cyclization process. The role of the phosphonate group was investigated by preparing the highly sensitive allenamide **6**[34] which decomposed after treatment with the CAN, leading to the conclusion that the phosphonate moiety is essential to stabilize allenamides and to promote this 5-*endo*-dig cyclization. The influence of the nitrogen atom directly attached to the allene moiety was evaluated with the allenylphosphonate **7**. In that case, the formation of the expected spirodienone lactam **8** did not occurred and only the decomposition of the starting material was observed (Scheme 2).

These results led us to propose the following mechanism: in the first step the *para*-methoxybenzyl ring is oxidized to the cyclohexadienone carbocation **9**.[35] Next, a 5-*endo*-dig cyclization leads to the formation of the iminium ion **10**. The nucleophilic addition of water to the latter followed by a prototropy transforms the phosphonate moiety as a leaving group leading to the lactam **3** and diethyl phosphite which is instantly degraded by the excess of CAN (Scheme 3).



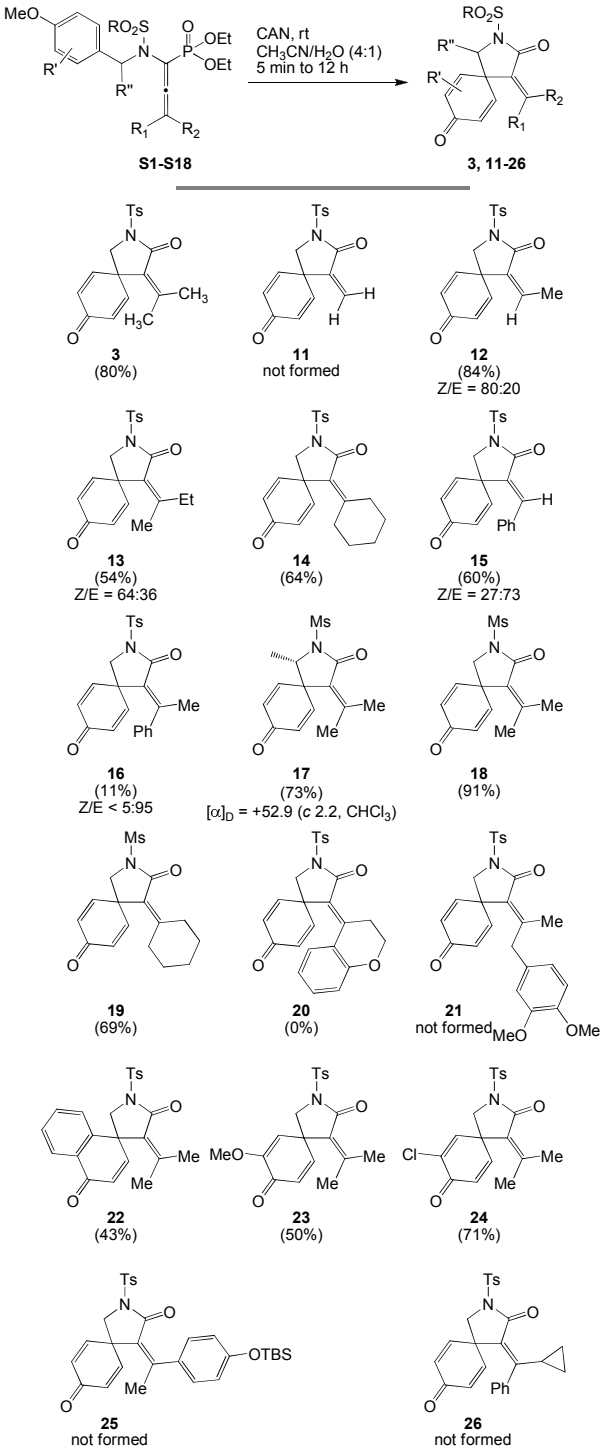
Scheme 2. Preliminary experiments to determine the mechanism for the spirodienone lactams formation.



Scheme 3. Proposed mechanism for the formation of the azaspirodienone **3**.

To explore the scope and limitations of this 5-*endo*-dig cyclization, a series of α-amino allenylphosphonates **S1-S18** (see supporting information) was prepared[31] and converted to the corresponding spirodienone lactams **11-26** by treatment with the CAN in a mixture of acetonitrile and water (2:1) (Scheme 4).

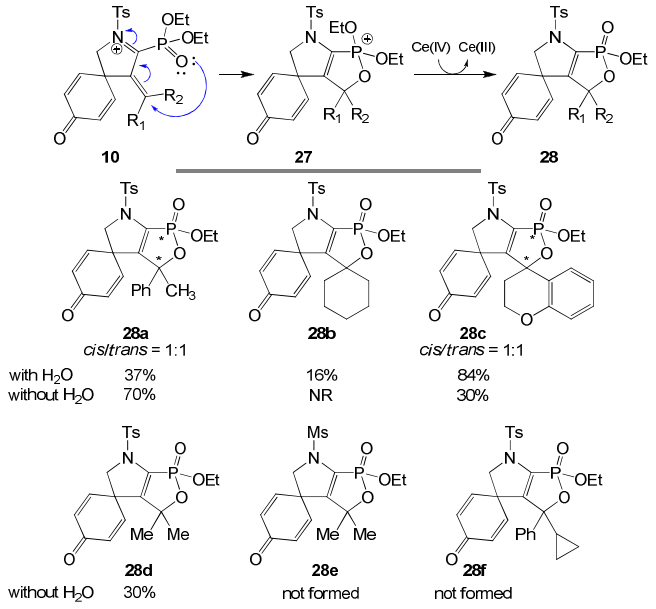
Although the reaction appeared to be general with possible modifications on the para-methoxybenzyl ring (compounds **23-24**), the sulfonamide (both tosylamide and mesylamide are transformed into the spirodienone lactam *eg.* **3** and **18**) and on the allene moiety, some spirodienone lactams were difficult to prepare. Indeed, despite all of our efforts, the spirodienone lactam **11** could not be prepared and only the decomposition of the starting material was observed. We postulated that with two hydrogen atoms on the allene moiety, the resulting iminium ion **10** was not stabilized and readily decomposed. The rate of this cyclization depends on the substituents on the allene moiety (5 min to 12 hours), indeed the time of the reaction was lowered with aromatic groups on the allene. The stereochemistry of the exocyclic double bond of compounds **12**, **13**, **15** and **16** was determined based on the chemical shift of the methyl group. Indeed, the carbonyl group of the lactam moiety, in **12**, induces a characteristic deshielding of the methyl group. It has to be noted that the substitution in α position from the nitrogen atom was also possible and led to the chiral lactam **17**. In the case of allenylphosphonates substituted with an aryl or benzyl ring bearing and alkoxy group, the formation of the corresponding spirodienone lactams **25** and **21** was not observed. This could be explained by a competitive reaction of this aromatic ring with the CAN, leading to the decomposition of the starting material. Decomposition was also observed during the formation of spirodienone lactam **26** bearing a cyclopropyl ring (Scheme 4).



Scheme 4. Scope and limitations of the 5-*endo*-dig cyclization

However, allenylphosphonates substituted with aryl groups showed, in some cases, an unexpected reactivity. Indeed, with a phenyl and a methyl group on the allene moiety the

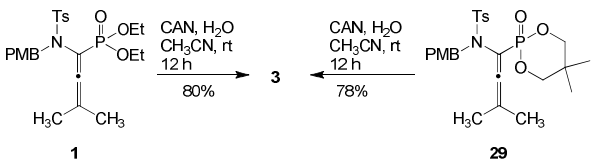
corresponding spirodienone lactam **17** was isolated in a low yield (11%, conv. 100%) and with an exclusive *E* selectivity. This selectivity could be explained by a π-stacking effect between the phenyl and the cyclohexadienone rings. In that case, the low yield of the 5-*endo*-dig cyclization is explained by the formation of a tricyclic organophosphorus compound **28a** which was isolated as the major product (37% yield). This unexpected reactivity was also observed during the formation of the spirodienone lactam **14**, which led to the formation of **28b** as a minor product (16% yield). Despite the complete conversion of the starting material, in the case of the α-AAP derived from 4-chromanone, the spirodienone lactam **20** was not formed. The tricyclic organophosphorus product **28c** was formed as a single compound in a high 84% yield. To explain the formation of the tricyclic phosphonates **28**, we postulated a competitive nucleophilic attack of the phosphonate moiety to the iminium ion **10**. The resulting intermediate **27** is next oxidized with the CAN to form the tricyclic spirodienones **28** in moderate to good yields (Scheme 5).



Scheme 5. Intramolecular attack of the phosphonate to the iminium **10**.

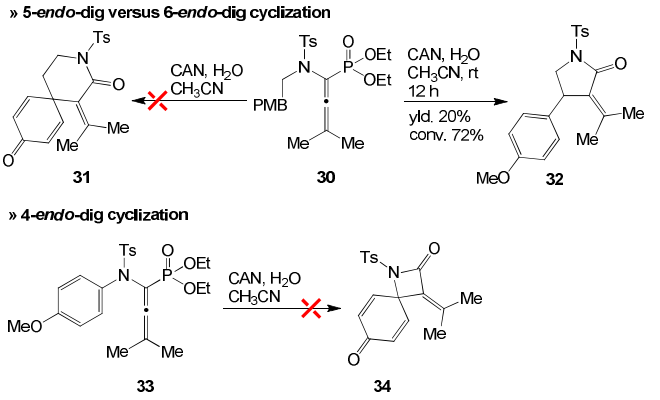
To favor the formation of the tricyclic phosphonates **28** we ran the reaction in acetonitrile without the addition of water. In that case, as expected, compound **28a** was formed in a higher yield (70%) and as a 1:1 mixture of stereoisomers. However, the scope of the reaction is limited. Indeed, without water the compound **28b** was not formed and the compound **28c** was formed in a lower yield (30%). Extension to other allenylphosphonates has been studied as well. However in these conditions only the tricyclic phosphonate **28d** was formed in a low 30% yield. The tricyclic phosphonates **28e** and **28f** could not be prepared through this approach leading to the decomposition of the starting material (Scheme 5).

Next, the influence induced by the nature of the alkyl groups on the phosphonate moiety, for the formation of the spirodienone lactam **3**, was investigated. We noticed that both α-amino allenylphosphonates **1** and **29** give the spirodienone lactam **3** in comparable yields (78 and 80%) (Scheme 6).



Scheme 6. Influence of the phosphonate leaving group on the cyclization.

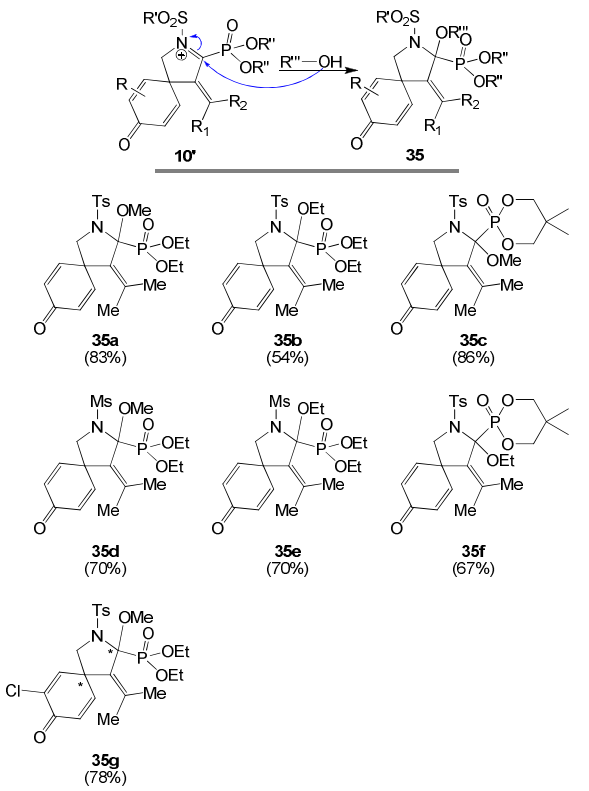
To enlarge the scope of this transformation we next explored the formation of the 6-membered ring lactam **31** through the cyclization of the allenylphosphonate **30** with CAN. However, in that case no 6-*endo*-dig cyclization was observed. Instead, the lactam **32** was formed in a low 20% yield and with an incomplete conversion of the starting material (conv. 72%). The formation of the latter is explained by the oxidation of the allenylphosphonate **30** with CAN to generate a benzylic carbocation which undergoes a 5-*endo*-dig cyclization. The formation of the spirodienone β-lactam **34** through a 4-*endo*-dig cyclization was studied as well starting from the *para*-methoxyphenyl derivative **33**. However in the presence of CAN the decomposition of the latter is observed (Scheme 7).



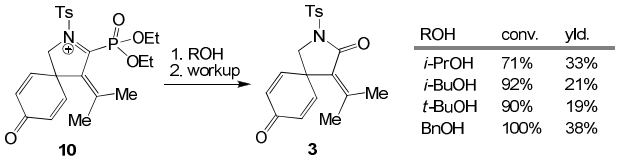
Scheme 7. Ring extension: 6-*endo*-dig and 4-*endo*-dig cyclization

Next, the nature of the nucleophile used to attack the iminium ion **10'** was investigated by replacing the water with an alcohol. The nucleophilic addition of MeOH and EtOH to the iminium **10'** (R_1=R_2=Me, R'=Tol, R''=Et) led respectively to the α-alkoxy α-aminophosphonates **35a** and **35b** in moderate to good yields. Using methanol as sole solvent, instead of a mixture of acetonitrile/methanol, slightly increased the yield from 61 to 70% for the formation of **35a**. Consequently, all the reactions for the formation of the α-alkoxy α-aminophosphonates **35** were conducted in alcohol as sole solvent (Scheme 8).

In contrast, the addition of sterically hindered alcohols to the iminium ion **10** failed to promote the formation of the corresponding α-alkoxy α-aminophosphonates **35**. Indeed, in that case a partial conversion of the starting material was observed and, after workup, the corresponding spirodienone lactam **3** was isolated (Scheme 9).



Scheme 8. Nucleophilic addition of alcohols to the iminium intermediate



ROH	conv.	yld.
i-PrOH	71%	33%
i-BuOH	92%	21%
t-BuOH	90%	19%
BnOH	100%	38%

Scheme 9. Addition of sterically hindered alcohols

In conclusion, we have reported a new approach for the formation of spirodienone lactams. Starting from readily available allenylphosphonates (3 steps from a sulfonyl *para*-methoxybenzyl amine) we were able to oxidize the *para*-methoxybenzyl ring, with the CAN, to promote a 5-*endo*-dig cyclization leading to a key iminium intermediate. This intermediate reacted with water to form spirodienone lactams. With an alcohol as solvent the iminium intermediate was transformed to α-alkoxy α-aminophosphonates. Without an external nucleophile, an intramolecular Michael type addition occurred leading to the formation a new type of tricyclic amino vinylphosphonates.

Notes and references

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