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Arylation of allylphosphonates and application to the preparation of phosphonomethyl-coumarin, -quinolinone and -benzoxepinone skeletons

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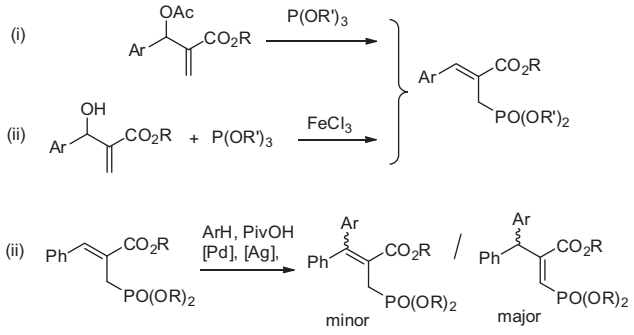
ABSTRACT

An efficient and selective synthesis of *Z*-(het)arylallylphosphonates is described. The versatile Pd-assisted process also allowed polyarylation sequences leading to star-shaped and binaphthyl derivatives. The methodology could be extended to the preparation of new phosphonomethyl-coumarin, -quinolinone, and -benzoxepinone architectures in high yields.

Introduction

Phosphonates are an important class of organic compounds that exhibit various bioorganic and medicinal properties such as antimicrobial, antimalarial, or enzyme inhibition.[1] The modulation of such properties can be envisioned through the installation of various substituents in α, β, γ-positions to the phosphonate group. In this context, 2-phosphonomethyl acrylates emerged as powerful intermediates, taking advantage of the twice-activated double bond induced by the presence of both phosphonomethylene and carboxylate groups. The installation of various (hetero)nucleophiles can thus take place through Michael-type additions leading to γ-substituted-2-phosphonomethyl acrylates.[2] The installation of aryl groups in γ-position of the phosphonate backbone is also of high interest giving access to cinnamylphosphonate derivatives. 3-Aryl-2-phosphonomethyl acrylates are usually considered as precursors of 3-phosphono-2-alkylpropionoic acid derivatives in model catalytic hydrogenation reactions.[3] The preparation of 3-aryl-2-phosphonomethyl acrylates rely mainly on Baylis Hillman strategy. Allylic acetates derived therefrom undergo addition of phosphorous-based nucleophiles to give stereoselectively the (Z)-3-aryl-2-phosphonomethyl acrylates (Scheme 1i).[4] 3-Substituted-2-phosphonomethyl acrylates can also be prepared by treatment of Baylis–Hillman adduct with $FeCl_3$ and trialkyl phosphites (Scheme 1ii).[5] Although limited to phenyl or dichlorophenyl aromatics, appealing arylation under Pd-catalyzed oxidative process has also been described recently (Scheme 1iii).[6]



Scheme 1. Main access to 3-aryl-2-phosphonomethyl acrylates.

We have been deeply involved in the construction of allylphosphonates bearing additional carboxylate groups and on further development of methods that rely on addition reactions.[2] We were interested in the installation of aromatics at the allylphosphonates **1** core through Pd-catalyzed arylation and whether the normal Heck-reaction course could be glanced to the construction of various fused heterocycles by using the carboxylate function located

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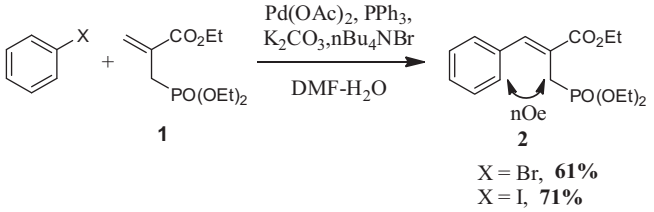
in position 1. In this context, the preparation of coumarin, quinolinone, and benzoxepinone skeletons[7] bearing a phosphonomethyl group is illustrated.

Results and discussion

We started to examine the arylation of allylphosphonate **1** through Heck-type reaction. Among the Pd source precursor, base, solvent, and additives tested, the catalytic combination using, $Pd(OAc)_2$, PPh_3, K_2CO_3, nBu$_4$NBr in DMF–H_2O was found superior. The optimal Pd/L ratio and reaction temperature were determined as 1/2 and 75 °C, respectively. Under these conditions, cinnamylphosphonate **2** could be obtained in 61% yield for 6h reaction courses. The yields could be further increased to 71% by using iodobenzene instead of the bromo analogue. Such optimized conditions avoided degradation of the starting phosphonate and appearance of side products rending tedious the silica gel purification step (Scheme 2).

The *E* configuration relative to the ethoxycarbonyl group was undoubtedly evidenced by NOESY two dimensional NMR spectroscopy.[8] The arylation process could be extended to various aromatics and heteroaromatics (Fig. 1). Indeed, *ortho*-tolyl, 1-naphthyl, and 2-thienyl fragments could be successfully installed in nearly 60% yield each. Further, we were able to couple three allylphosphonates moieties at a central benzene ring using 1,3,5-tribromobenzene as starting electrophile affording an appealing star-shaped architecture.

Under the same reactions conditions, 2 equivalents of allylphosphonate **1** reacted with 1,8-diiodonaphthalene to form symmetrical functionalized biaryl **7** in 68% yield. The latter plausibly arose from a sequential installation of the naphthyl group in position 3 of the starting allylphosphonate leading on a mono coupled intermediate and a further Pd-promoted homocoupling reaction affording the binaphthyl unit.

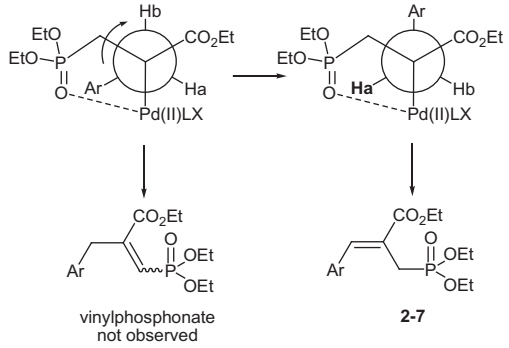


Scheme 2. Phenylation of allylphosphonate **1**.

The few examples that describe a palladium catalyzed arylation of allylphosphonate reported the formation of vinylphosphonate as final product[9] or a mixture of vinyl and arylallylphosphonate[6] after the β-elimination process.

Interestingly, products **2**–**7** were isolated as unique products of the transformation. As shown in Scheme 3, selective β-Ha elimination takes place leading the formation of the functionalized styrene rather than the vinylphosphonate and accounts for the stereochemistry observed. As already stated by Kim,[10] stabilization of the carbopalladate-intermediate by the phosphonate group plausibly controls the β-H elimination process. Indeed, hydrogens located α to the phosphonate group within the pseudo metallacycle are difficult to adapt the mandatory syn-position with respect to the palladium center. As a consequence the easier β-Ha elimination takes place affording the expected styrene product.

We next examined the Pd-promoted installation of *ortho*-substituted iodoarenes and focused especially on iodophenol and iodobenzylalcohol. At first, iodophenol reacted under the aforementioned catalytic conditions at room temperature to cleanly afford the expected arylallylphosphonate **8** in a fair 62% yield. Attempts to increase the yield by reacting both starting material at 70 °C unexpectedly led to the formation of coumarin derivative **9**. The preparation of such coumarin has been described by two synthetic methods. The first was done through multistep processes characterized by the installation of the 'P-based' group in the last step of the sequence by reacting triethyl phosphite with 3-(iodo) and 3-(chloromethyl)coumarins.[11] The second pathway started from 3-(diethoxyphosphoryl)propionic acid. Further exposure to the action of oxalyl chloride and salicylaldehyde under basic conditions led to the designed coumarin (Scheme 4).[12]



Scheme 3. Phosphonate-assisted regioselective β-elimination process.

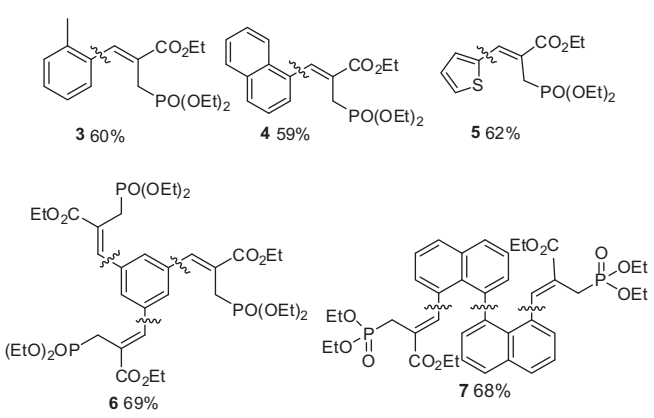
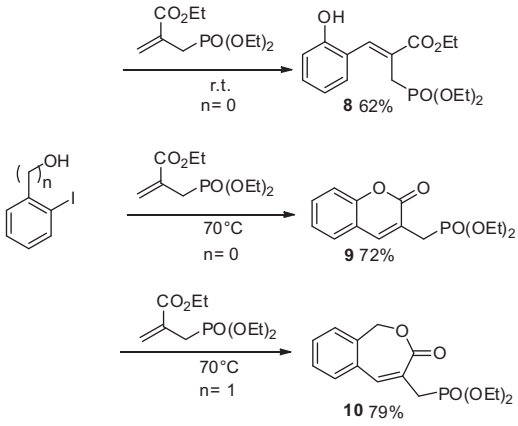
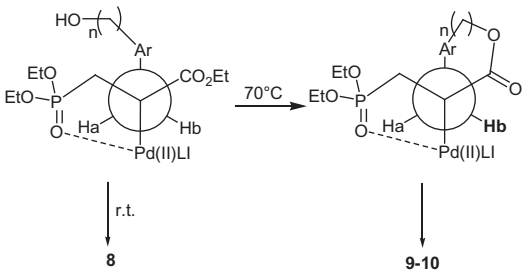


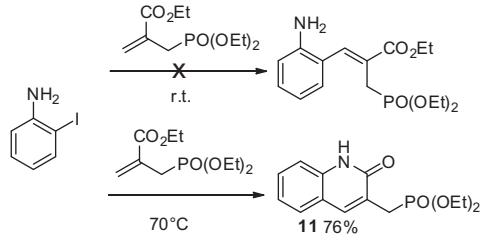
Figure 1. Pd-catalyzed installation of various (hetero)aromatics to allylphosphonates.



Scheme 4. Selective access to phosphonomethyl-hydroxystyrene, -coumarin, and –benzoxepinone structures.



Scheme 5. Intermediates involved in the formation of heterocyclic derivatives.



Scheme 6. Preparation of phosphonomethyl-quinolinone.

Similarly, lactone **10** was obtained in a high 79% yield under similar reaction conditions. Interestingly, the formation of both six- and seven-membered heterocycles have been obtained regardless of the ring size leading to novel phosphonomethyl-substituted fused-heterocycles.

The formation of fused heterocycles **9**–**10**, most probably arises from a similar pathway involving the stabilized intermediate which is first produced through the carbopalladation process. The latter might then evolve depending on the reaction temperature and on the nucleophile. At room temperature, the Pd-intermediate leads to the arylallylphosphonate **8** in the iodophenol series (Scheme 5). In contrast, at 70 °C the intermediate is transformed into a lactone moiety which enforced one conformation and gave the corresponding heterocycles **9** and **10** after β-Hb elimination step regardless of the hydroxyl precursor. Although isomerization from the *E* to *Z* olefin after classical β-H elimination cannot be fully ruled out, we exclusively isolated the *E* configuration for compounds **2**–**5** under the same conditions, which corroborates our hypothesis illustrated in Scheme 5.

Encouraged by these results, we tried to extend our methodology to lactam analogues. Thus iodoaniline was next reacted with allylphosphonate **1** in the presence of $Pd(OAc)_2$, PPh_3, K_2CO_3, and nBu_4NBr in DMF–H_2O. Disappointingly, at room temperature, the expected arylallylphosphonate could not be isolated both reactants being almost completely recovered. In contrast, increasing the reaction temperature to 70 °C led to the formation of 2-quinolinone **11** in 76% yield (Scheme 6).

In conclusion, we succeeded in the selective preparation of arylallylphosphonates. The Pd-assisted process is versatile allowing the installation of various aromatic and heteroaromatic groups at the allylphosphonate core. Polyarylation could also be obtained leading to star-shaped benzene derivatives. The styrene fragment is selectively obtained in a *E* configuration through phosphonate-driven regiodiscrimination of the β-H elimination. The methodology could be further extended to the preparation of new phosphonomethyl-coumarin, -quinolinone, and -benzoxepinone architectures in high yields.

Acknowledgments

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Supplementary data

Supplementary data (experimental details as well as characterization data and copies of NMR spectra) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.02.038.

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