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Synthesis of spiro-pyridones and spiro-quinolones by sequential palladium on carbon-catalyzed allylation and ring closing metathesis reactions

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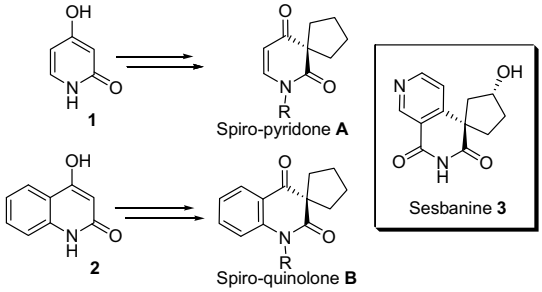
ABSTRACT

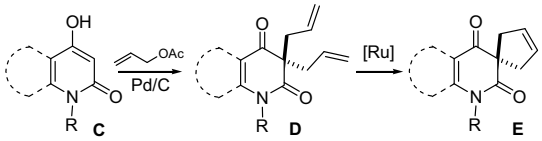
A rapid and efficient strategy for the preparation of spiro-pyridones and spiro-quinolones using sequential Pd(0)/C-catalyzed allylation and ring closing metathesis reactions is described. The developed protocol features a fully regioselective allylation at C3 taking advantage of the unusual reactivity of Pd(0)/C catalyst. Application of the present methodology in nucleoside chemistry has also been investigated.

The development of rapid and practical synthetic strategies directed at the preparation of structurally original frameworks and scaffolds is of great importance in the context of drug discovery.[1] As part of a program focusing on the chemistry and biology of 4-hydroxy-2-pyridones and 4-hydroxy-2-quinolones, we were interested in the transformation of such skeletons into spiro-pyridone **A** and spiro-quinolone **B** whose structures are related to natural product sesbanine **3** (Scheme 1). Although sesbanine **3** is only weakly cytotoxic,[2] we considered that its unusual structure could serve as an interesting lead for the discovery of new antitumor agents. Such a strategy has been successfully applied during a total synthesis campaign of migrastatin in Danishefsky laboratories.[3]

This Letter describes the expedient synthesis of spiro compounds making efficient use of our recently reported Pd(0)/C-mediated allylic alkylation[4] in combination with a ring-closing metathesis[5] (Scheme 2). In addition, we demonstrated that the present methodology could be extended to the preparation of novel nucleosides related to the 3-deazauridine.



Scheme 1. Overall strategy.



Scheme 2. Sequential Pd(0)/C-catalyzed allylation-RCM reactions.

Our strategy required first the preparation of diallylic compounds. Although trivial in appearance, it is well documented that the C_3,C_3-dialkylation of 4-hydroxy-2-quinones and 4-hydroxy-2-pyridones under basic condition is mostly accompanied by important formation of O-alkylated and O,C_3-dialkylated by-products.[6] As a consequence, we regarded these substrates as β-dicarbonyl compounds which should react as nucleophiles under palladium-catalyzed allylation. Actually, a single report makes efficient use of a 4-hydroxy-2-pyridone system for palladium-mediated selective mono-alkylation at C_3.[7] However, to the best of our knowledge, there is no described method for an efficient and selective C_3,C_3-diallylation. We recently, reported that Pd(0)/C (or Pd(II)/C) could be used as practical and efficient heterogenous catalyst for allylic alkylation of various nucleophiles.[4] We noticed that cyclic diketones such as Meldrum's acid **4** gave only the product **5** resulting from a double alkylation with good yield even when the nucleophile was used in excess. The same reactivity was not observed under homogeneous conditions where the mono-alkylated product **6** was the major isolable compound (Scheme 3).[8]

With the aim of exploiting the interesting reactivity of Pd(0)/C, we selected the 4-hydroxy-2-pyridones **7a** and **7b** as model substrates for reaction with allyl acetate under Pd(0)/C catalysis (Table 1).

When Ph_3P was omitted, only trace amount of the desired product was observed along with a number of unidentified by-products (entry 1). The phosphine acts as a stabilizing agent for palladium, generating in situ a more reactive Pd(0)–Ph_3P complex. It is likely that palladium nanoparticles, leached from the support, are the

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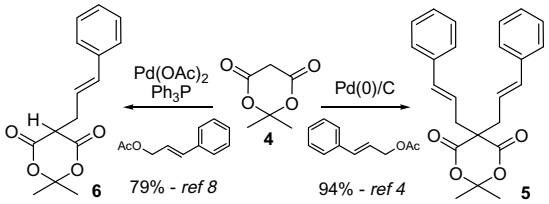
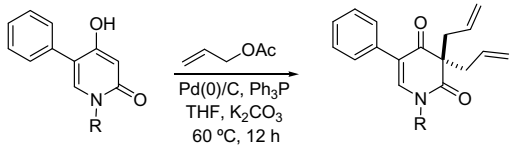


Scheme 3. Dual reactivities of heterogeneous versus homogeneous Pd catalysts.

Table 1
Optimizations studies



Entry	Pyridone	Ph_3P (equiv)	Pd(0)/C (equiv)	Allyl acetate (equiv)	Product	Yield[a] (%)
1	**7a**	—	0.05	2.2	—	—
2	**7a**	0.2	—	2.2	—	—
3	**7a**	0.2	0.05	2.2	**8a**	50
4	**7a**	0.2	0.05	4	**8a**	78
5	**7b**	0.2	0.05	2.2	**8b**	50
6	**7b**	0.2	0.05	6	**8b**	69

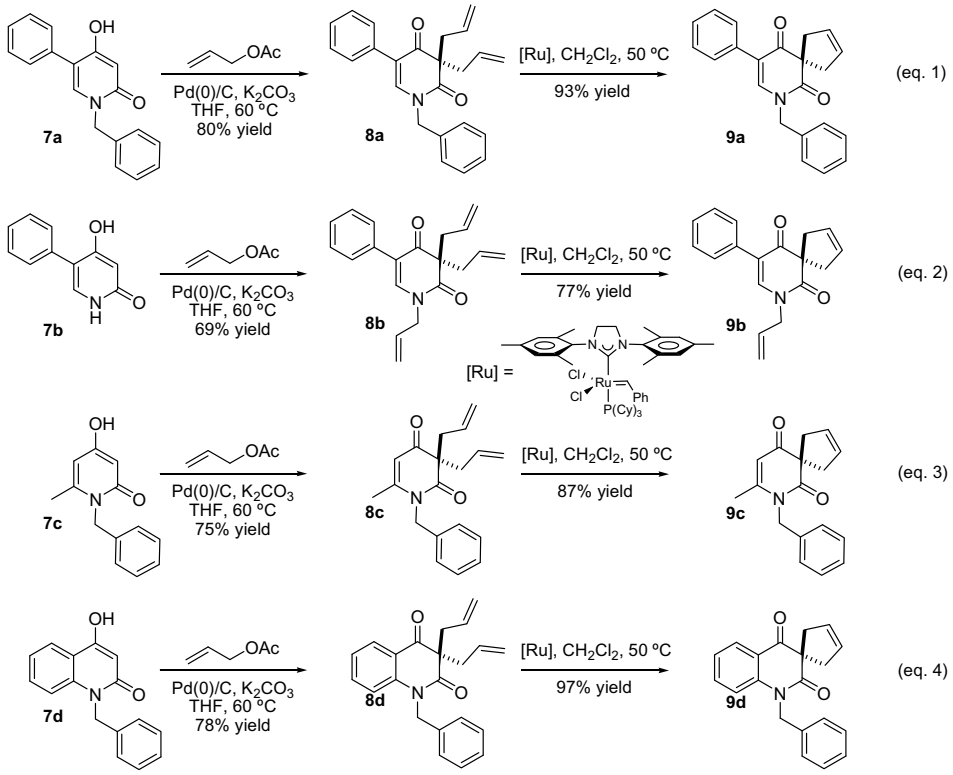
[a] Isolated yields.

true catalytic active species that required Ph_3P as stabilizing ligand as already observed for other Pd-catalyzed cross-couplings.[9] However, at the end of the reaction, low palladium level (<10 ppm) was measured by ICP-MS in the solvent indicating a dissolution–reprecipitation process also called the boomerang effect. Although palladium-free allylic alkylation has recently been reported,[10] in our case no reaction occurred in the absence of Pd(0)/C, where starting material was quantitatively recovered (entry 2). This result indicates a genuine Pd(0)/C-catalyzed reaction. As expected, a double allylation occurred regioselectively at C3 with good yield (78%) when an excess of allyl acetate was used (entry 4). Interestingly, unprotected pyridone **7b** was not only diallylated at C3 but also selectively at the nitrogen atom, with no detectable O-allylated by-product, with an exploitable yield (69%). It should be noted that even when an excess of pyridone **7b** was used, the tri-allylated compound was isolated as the major compound. From these preliminary results, it should be noted that O-allylation compounds were never observed from the crude reaction mixtures.

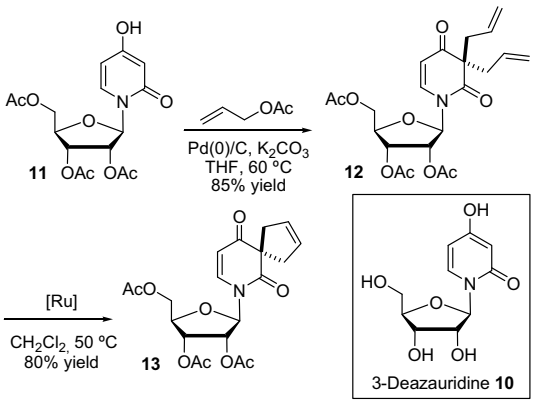
To further explore the scope of this transformation, we selected a variety of pyridone- or quinolone-based nucleophiles **7a–d** for reaction with allyl acetate under Pd(0)/C-mediated catalysis. The results compiled in Scheme 4 clearly highlight the efficiency of this two-step transformation. As expected, O-allylation compounds were never observed from the crude reaction mixtures, and the targeted compounds **8a–d** were, in all cases, the only isolable products. The subsequent RCM reaction on compounds **8a–d** proceeded smoothly with high yield to give spiro-compounds **9a–d**. It should be pointed out that the first-generation Grubbs catalyst was ineffective for this transformation leaving the diallylic compounds **8a–d** unaltered.

In order to further illustrate the synthetic utility of the sequential allylation-RCM reactions for the rapid elaboration of spiro heterocycles of potential biological importance, we prepared a spiro analogue of the 3-deazauridine **10** (DU), (Scheme 5).

It has been shown that DU **10** inhibits cytidine trophosphate synthase, thereby reducing intracellular levels of cytidine triphosphate and disrupting DNA and RNA syntheses.[11] Although DU **10**



Scheme 4. Scope of the protocol.



Scheme 5. Preparation of a spiro nucleoside.

used as a single agent exerts negligible clinical efficiency resulting in a lack of interest in clinical investigation,[12] it has been recently disclosed that DU in combination with retinoic acid or dibutyryl cyclic adenosine monophosphate (dbcAMP) induces cell death by apoptosis in myeloid HL-60 cells.[13] Moreover, our own investigations on the preparation of novel nucleosides derived from DU **10** indicated that such a skeleton has potent antiviral activities.[14] We were pleased to find that our methodology proceeded in good yield (68% over two steps) to furnish the new spiro analogue **13** of DU **10**. The mild conditions of the two steps seem particularly relevant for sensitive substrates such as nucleosides.

In summary, we have disclosed along these lines a rapid and efficient method for the construction of new spiro heterocycles. The method features an unusual Pd(0)/C-mediated highly regioselective diallylation at C3, which allows minimal contamination of the products by palladium residues, followed by a ring closing metathesis. We are currently exploring other applications of this strategy in the chemistry of nucleosides. Detailed biological activities of various libraries of compounds will be disclosed in due time.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.11.026.

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14. Results to be patented.