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A new route to acyclic nucleosides via palladium-mediated allylic alkylation and cross-metathesis

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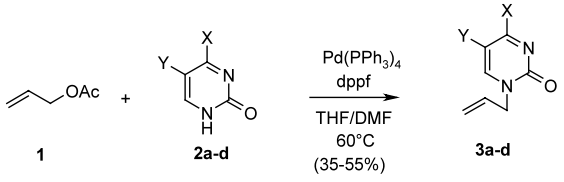
Abstract—A method for the syntheses of *E*-unsaturated acyclic nucleosides via a combination of palladium-catalyzed allylic alkylation and ruthenium-based cross metathesis is described. This approach provides a concise, efficient and reliable route to new nucleoside analogues.

Interest in acyclic nucleosides began in the mid-1970s when Acyclovir (ACV) was first reported as a potent anti-herpes drug.[1] The unprecedented selectivity of ACV as an anti-viral drug and the subsequent clarification of its mode of action towards virally coded enzymes provided massive impetus for further synthesis of related compounds and investigation of their biochemical fate.[2] The use of palladium-catalyzed allylic alkylation[3] (Tsuji–Trost reaction) and olefin cross-metathesis[4] have proven to be powerful and versatile procedures which have gained recognition due to their broad scope. To the best of our knowledge, a combination of these two important reaction types has not yet been employed in the synthesis of unsaturated acyclic nucleosides. To date, only one application by Freer et al.[5] has reported the chemical synthesis of acyclic nucleosides by utilizing a palladium-catalyzed allylation. In general such unsaturated acyclic nucleosides can be synthesized from a protected glyceraldehyde using a Wittig–Horner–Emmons reaction; nevertheless, the *Z*-α,β-unsaturated ester was obtained exclusively, without any trace of *E*-isomer.[6] Thus, as part of our drug discovery program, this contribution reports a straightforward synthesis of hitherto unknown unsaturated acyclic nucleosides by a tandem catalytic process involving a ruthenium-based metathesis as well as a palladium-catalyzed allylic alkylation.

The first step of this chemical pathway consists in the regioselective synthesis of *N*-allyl derivatives of nucleobases, which could be obtained from alkylation of the heterocyclic ring with 1,2-dibromoproane followed by dehydrobromination.[7] Nevertheless, the reported poor yields prompted us to examine the Pd(0)-catalyzed reaction of allylic acetate with various pyrimidines (Table 1).

According to the literature,[8] reaction of uracil **2a** with allyl acetate **1** in the presence of freshly prepared $Pd(PPh_3)_4$ and dppf [(1,1′-bis(diphenylphosphinoferocene)], led to a 4/1 mixture of *N*-1 monoallylated **3a** and the *N*-1,*N*-3-diallylated analogue in a yield of 45% (entry 1). When using 6-methyluracil **2b**, only the *N*-1 allylation to **3b** was observed in a 55% yield (entry 2).

Table 1. Palladium-catalyzed allylation of pyrimidines



1 2a-d 3a-d

Entry	Nucleobase	X	Y	Product	Yield (%)
1	**2a**	OH	H	**3a**	45[a]
2	**2b**	OH	CH_3	**3b**	55
3	**2c**	OH	I	**3c**	35
4	**2d**	NHBz	H	**3d**	45

[a] Total yield: formation of a 4/1 mixture of monoallylated and diallylated compounds separable by chromatography.

Keywords: palladium-mediated allylic alkylation; cross-metathesis; acyclonucleosides.
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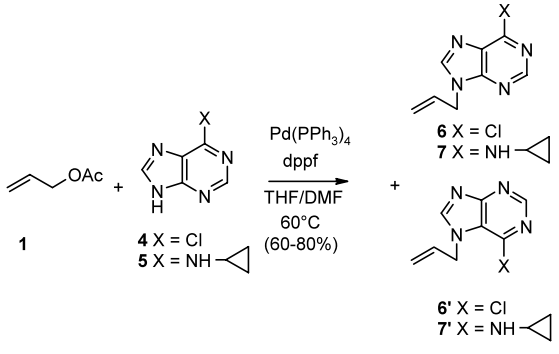
Application of the same procedure with iodouracil **2c** and *N*-4-benzoylated cytosine **2d** afforded selectively the monoallylated products **3c**[9] and **3d** in 35 and 45% yields, respectively (entries 3 and 4).

The Pd-catalyzed coupling of an allylic acetate with a purine base can, in principle, lead to a mixture of *N*-7 and *N*-9 regioisomers. This problem, which is classic in Vorbrüggen coupling of purines with sugars,[10] has been recognized only recently in Pd(0)-catalyzed couplings. Gundersen et al.[11] reported that the coupling of purines with allylic esters led to a mixture of regioisomers, the ratio of which could be modified by incorporation of larger groups at the 6-position of the purine. The best compromise, in agreement with Crimmins' work,[12] was obtained with a 6-chloropurine analogue **4** or a 6-aminocyclopropylpurine derivative **5** leading, in our hands, to a mixture of *N*-9 isomer **6** and *N*-7 isomer **6′** (determined by ^{1}H NMR) in a 3/2 ratio and **7** as the only *N*-9 derivative, respectively (Table 2).

With these allylic heterocycles in hand and with the aim of synthesizing acyclic nucleosides using an efficient procedure, we turned our attention to establishing the best conditions for a cross-metathesis reaction. In this area, we[13] and others[14] have mainly used a ruthenium-mediated metathesis for the synthesis of carba- or labelled nucleosides. Based on our previous results illustrating the user-friendly character of ruthenium-carbene species bearing one imidazol-2-ylidene ligand **8**[15] and its proven tolerance towards an array of polar groups (particularly the amide group), we were prompted to probe the performance of **8** in this specific application.

Thus, reacting the protected allylic diol[16] **9** with allylic pyrimidine derivatives **3a–d** in the presence of catalytic amounts of **8** in refluxing dichloromethane delivered

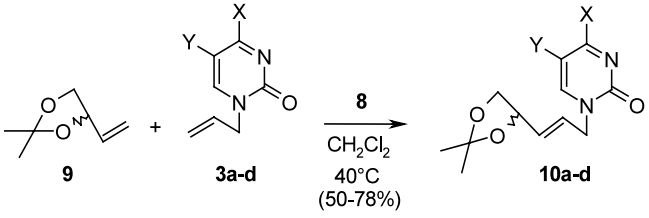
Table 2. Palladium-catalyzed allylation of purines

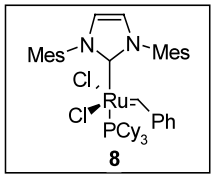


Entry	Nucleobase	X	Ratio *N*-9/*N*-7[a]	Yield (%)[b]
1	**4**	Cl	**6**:**6′** 3/2	80
2	**5**	NH	**7**:**7′** 1/0	60

[a] Regioisomers separable by chromatography.
[b] Total yield for the two regioisomers.

Table 3. Synthesis of acyclic nucleosides via cross-metathesis reaction between protected diol **9** and allylic base **3**



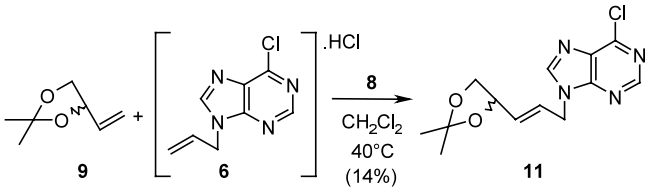


Entry	Compound	X	Y	Product	Yield (%)
1	**3a**	OH	H	**10a**	78
2	**3b**	OH	CH_3	**10b**	50
3	**3c**	OH	I	**10c**	56
4	**3d**	NHBz	H	**10d**	57

the target acyclic nucleosides **10a–d**,[17] respectively, in good to moderate yields (Table 3). No self-metathesis products were observed. The cross-metathesis product stereochemistry was confirmed by ^{1}H NMR. Only the *E*-stereoisomer was obtained.

Even more challenging was the cross-metathesis of protected allylic diol **9** with allylic purine **6**, due to the presence of several tertiary basic nitrogens. The tolerance of the ruthenium metathesis catalyst towards basic tertiary amines is less understood as most examples reported in the literature use a deactivated nitrogen (amide, carbamate, sulfonamide).[4] Tertiary basic nitrogen probably interferes with the catalytic cycle by coordination to the ruthenium. To circumvent this problem, the deactivation of the basic nitrogen of purine is imperative before the final metathesis step. However, only a few literature reports describe and/or propose a solution to this problem. It is noteworthy to mention that no previous report has appeared tackling this issue with the purine system. To address this issue, we either used PTSA[18] (*p*-toluenesulfonic acid) to form a tosylate salt or protonated the basic nitrogens with HCl.[19] However, after optimization, the addition of HCl to **6** gave the best results, leading to the purine acyclonucleoside **11**[20] (14%) in the presence of starting material (Scheme 1).

These results led us to investigate an alternative synthetic route, utilizing first the cross-metathesis step leading to an allylic acetate which then could be used in

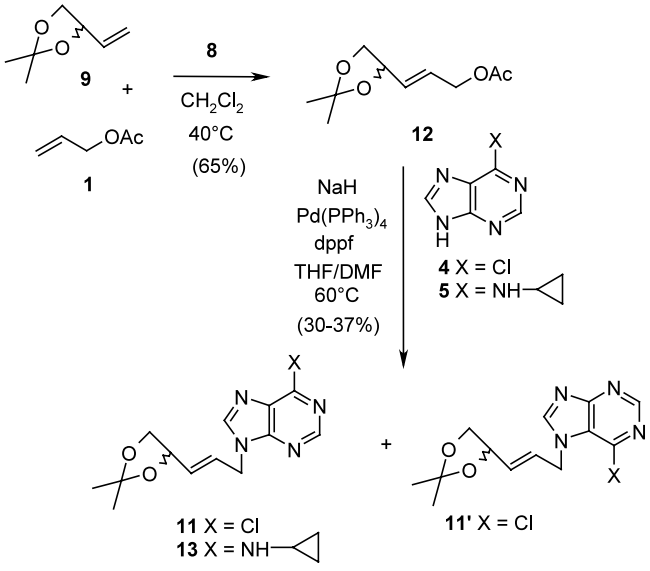


Scheme 1. Synthesis of acyclic nucleosides via cross-metathesis reaction in the purine series.

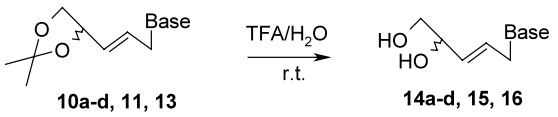
the palladium-mediated allylic allylation of a nucleobase (Scheme 2).

Thus the straightforward cross-metathesis of **9** with allyl acetate **1** in the presence of catalyst **8** afforded the expected acetate **12**[21] in 65% yield; it is important to mention here that some homodimeric compounds obtained from the self-metathesis of **9** and of **1**, respectively, were isolated. Subsequent treatment of **12** with 6-chloropurine **4** under Tsuji–Trost Pd(0) allylation conditions afforded a 1:1 mixture of *N*-9/*N*-7 isomers **11** and **11′** (easily separated by column chromatography on silica gel) in an overall yield of 37%. Meanwhile, by applying the Pd(0) allylation conditions to the 6-aminocyclopropyl purine **5**, the *N*-9 regioisomer **13** was the only product isolated in moderate yield (30%). Finally, to complete the synthesis of unsaturated acyclic nucleosides, the acetonide protecting groups of **10a–d**, **11** and **13** were removed by treatment with a mixture of TFA/H_2O (1:2, v/v) affording the acyclic nucleosides **14a–d**, **15** and **16**, respectively, in quantitative yields (Scheme 3).

In summary, a new and efficient route to hitherto unknown unsaturated acyclic nucleosides has been



Scheme 2. Alternative synthesis of unsaturated purine acyclonucleosides **11**, **11′** and **13**.



Scheme 3. Deprotection step.

developed based on two metal-mediated transformations: a palladium(0) catalyzed coupling of a nucleobase and an allylic acetate side chain and a ruthenium-based cross-metathesis. Extension of this strategy to the preparation of other systems, which may represent a new class of drugs and/or tools for chemical biology, is currently in progress in our laboratories.

Acknowledgements

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