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A new palladium(II)-catalyzed [3,3] aza-Claisen rearrangement of 3-allyloxy-5-aryl-1,2,4-oxadiazoles

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ABSTRACT

A new efficient palladium(II)-catalyzed [3,3] aza-Claisen, formal sigmatropic rearrangement of 3-allyloxy-5-aryl-1,2,4-oxadiazoles was developed. The mechanism was studied by analyzing the regiochemical and stereochemical course of the reaction. The results obtained indicated the intervention of a cationic pallada-cycle similar to the one postulated for the Cope rearrangement of 1,5-dienes.

The [3,3] aza-Claisen rearrangement is a sigmatropic process that involves an allylic transfer in *N*-allyl, *N*-vinyl amines, or related systems that leaves to the formation of γ,δ-unsaturated imines.[1] It was efficiently employed in a number of useful transformations such as the stereospecific synthesis of 2′,3′-dideoxynucleoside precursors.[2]

Pd(II) salts are known to catalyze many synthetically useful formal [3,3]-sigmatropic rearrangements in 1,5-dienes,[3] allyl vinyl ethers, and also in aza-Claisen-type processes involving allylic imidates and some allyl-substituted heterocyclic frameworks, that include 2-allyloxypyridines,[4] 5-allylthio-1,2,4-triazin-3(2*H*)-ones,[5] 4-allylthiopyrimidin-2(1*H*)-ones,[5] and 2-(allylthio)pyrimidin-4(3*H*)-ones.[6] Recently, a chiral Pd(II) catalyst, (*S*)-COP-Cl has been used in an interesting enantioselective [3,3] rearrangement of allyloxypyridines and other related heterocycles.[7]

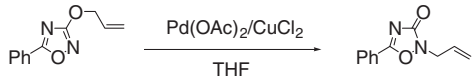
On the other hand, 1,2,4-oxadiazoles present many applications in medicinal chemistry,[8] such as peptidomimetics and enzyme inhibitors,[9] apoptosis inducers,[10] or as unnatural bases in the extension of DNA strands.[11] Among these, N(2)-substituted 1,2,4-oxadiazolones represent an emerging class of bioactive molecules,[12] mainly represented by the quisqualic acid, the sole natural 1,2,4-oxadiazole, responsible for the QUIS effect, that is, the agonist effect toward a number of amino acid receptors in the SNC.[13]

In light of this, in this Letter we describe a new Pd(II)-catalyzed [3,3] aza-Claisen rearrangement involving 3-allyloxy-1,2,4-oxadiazoles to give the related N(2)-substituted 1,2,4-oxadiazol-3-ones.

In a preliminary set of experiments 3-allyloxy-5-phenyl-1,2,4-oxadiazole **1a** was reacted with palladium acetate ($Pd(OAc)_2$) and $CuCl_2$ at different molar ratio and temperatures, following a 2^3 factorial experimental design (Table 1), in order to deduce the best reaction conditions for the obtainment of the rearranged compound **2a**.

The reaction shows an high sensitivity toward the presence of Cu(II), as it can be seen comparing entries 1–4 with 5–8. Further, from the data reported in Table 1 it can be deduced that the effect of temperature is dramatic when Cu(II) is present (entries 5,7 and 6,8) while it is substantially negligible when Cu(II) is absent

Table 1
Optimization of the reaction conditions[a] for the rearrangement of compound **1a** to **2a**



1a **2a**

Exp. No.	$Pd(OAc)_2$ (mol %)	*T* (°C)	$CuCl_2$ (equiv)	Yield[b] (%)
1	5	25	—	17
2	10	25	—	38
3	5	50	—	25
4	10	50	—	30
5	5	25	5	52
6	10	25	5	70
7	5	50	5	95
8	10	50	5	97

[a] All the reactions were performed by mixing **1a** 0.07 M in dry THF (3 mL) with $Pd(OAc)_2$ and $CuCl_2$ and stirring the solution for 12 h.
[b] Isolated yields.

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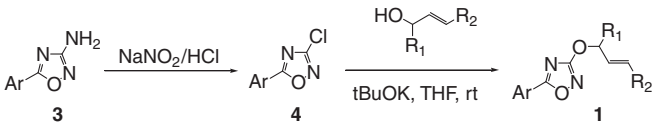
(entries 1,3 and 2,4). Finally, the effect of an increase in the Pd(II) concentration from 5% to 10% mol/mol is negligible at 50 °C in the presence of Cu(II) (entries 7 and 8). The un-catalyzed reaction was quite ineffective as no detectable amount of transposed product **2a** was found after refluxing a solution of **1a** and $CuCl_2$ in THF for 24 h. Hence, all of the subsequent experiments were carried out at the experimental conditions corresponding to entry 7 of Table 1.[14]

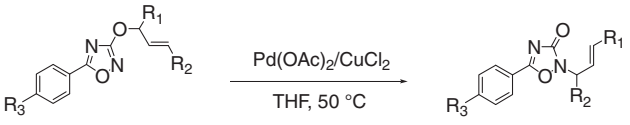
In order to get further information concerning the mechanism of the reaction, we prepared a set of 3-(2′-alkenyloxy)-5-aryl-1,2,4-oxadiazoles **1b–g**, by a known procedure starting from the 3-amino-5-aryl-1,2,4-oxadiazoles **3** (Scheme 1).[15] These compounds were converted to the corresponding 3-chloro-5-aryl-1,2,4-oxadiazoles **4** by in situ diazotization/chlorination with $NaNO_2$/HCl.[16] Then the desired 3-(2′-alkenyloxy) derivatives were obtained by reacting the chloro-derivatives with the necessary alkoxide.

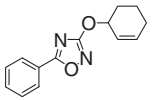
The compounds **1b–g** were subjected to the reaction conditions previously optimized for the transposition of compound **1a**



Scheme 1. Synthesis of the 3-(2′-alkenyloxy)-5-aryl-1,2,4-oxadiazoles **1**.

Table 2
Results of the transposition reaction of compounds **1a–g**



Entry	Compound	R_1	R_2	R_3	Yield[a] (%)
1	**1a**	H	H	H	95
2	**1b**	Me	H	H	79
3	**1c**	H	Me	H	86
4	**1d**	H	Ph	H	64
5	**1e**				33
6	**1f**	H	H	MeO	62
7	**1g**	H	H	NO_2	45

[a] Isolated yields, reaction conditions as in note 14.

(5 mol % Pd(II), 5 equiv Cu(II), at 50 °C, Table 2), to give the transposed products **2**.[14] The results are summarized in Table 2.

The reaction yields range from 45% to 95%. In the case of the more sterical demanding cyclohexyl-substituted compound **1e**, the yield dramatically dropped to 33%.

The transposition process occurs with quite complete regioselectivity, as it can be seen from the formation of the *N*(2)-2′-(*E*)-butenyl-substituted product **2b** and the *N*(2)-1′-alkyl-substituted products **2c**,**d**.

Moreover, a very high degree of stereoselectivity was observed in the case of the substrate **1b** that exclusively gave rise to the formation of the compound **2b** with a 100% *E* stereochemistry of the side chain double bond.

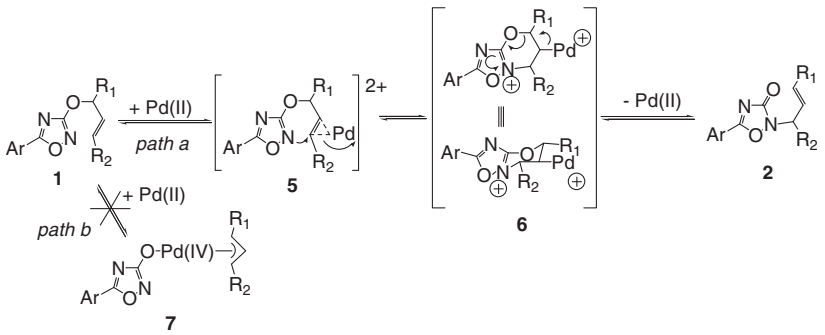
Two alternative possible reaction pathways (Scheme 2) were postulated by analogy with the well known palladium-catalyzed Cope transposition reaction.[17]

In the *path a*, a nucleophilic attack by the *N*(2) on the Pd(II)-η^2-coordinated double bond, in the intermediate **5**, brings to the formation of a six members cationic pallada-cycle **6** that accounts for the observed regioselectivity. This intermediate, in turn, is opened by an *anti*-β-Pd,O-elimination step to give the final product. The pseudoequatorial disposition of the methyl-substituent in the cyclic intermediate accounts for the observed stereoselectivity in the formation of compound **2b**.

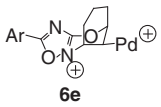
The alternative *path b*, that would involve an initial oxidative addition step to give an unusual η^3-allyl-Pd(IV) intermediate **7**, can be ruled out as it should bring to the formation of the same regioisomer (or mixture of) starting from both the compounds **1b**,**c**. This kind of Pd(IV) intermediates were postulated in the Cope rearrangement of some 1,5-dienes in oxidative conditions, in the presence of the Pd(II)/Cu(II) catalytic system,[17a] that may occur via a mechanism involving a bis(η^3-allyl)Pd(IV) intermediate, as it was deduced by the authors on the ground of both reasonable theoretical considerations and strong experimental evidences.

Further, the beneficial effect of the presence of Cu(II) in the reaction media could be ascribed to an oxidative stabilization of the pallada-alkyl cation toward the possible β-hydride reductive elimination, with acetate anion acting as a base. This hypothesis is enforced by the appearance of the 'black-palladium' within the reaction vessel, indicative of the occurrence of a Pd(II)/Pd(0) reduction process, that accompanies the decrease of the yield in the transformation of **1a** performed without Cu(II) (Table 1). This observation is in agreement with an evidence reported by Lei et al.[18] that showed how Cu(II) is effective in promoting the oxidative cleavage of the carbon–palladium bond (see the conversion of the intermediate **6** to the product **2**, Scheme 2) preventing the possible β-hydride elimination-Pd(II)/Pd(0) reduction to occur and prompted us to choose a Cu(II) salt as a co-oxidant.

In summary, the whole of the data collected seems to indicate the operation of the reaction mechanism depicted in *path a*



Scheme 2. Mechanism of the transposition reaction.



6e

Figure 1. Proposed structure for tricyclic intermediate **6e**.

(Scheme 2). As a consequence, the loss of efficacy observed in the formation of the cyclohexyl-substituted compound **2e** can be explained by the formation of a sterically congested bridged [4,3,1] bicyclic intermediate **6e** (Fig. 1).

Moreover, a comparison between the reactivity of compounds **1a**, **1f,** and **1g** shows as the reaction efficiency is not related to the electronic character of the 5-aryl substituent, as a decrease of the reaction yield occurs with both the electron-withdrawing –NO_2 group and with the electron-releasing –OMe group. In the event that this decrease is only due to a negative kinetic effect, it can be rationalized taking into account the lack of co-planarity between the two aromatic rings, as it was observed previously by X-ray crystallography.[19]

In conclusion, a new efficient palladium(II)-catalyzed [3,3] aza-Claisen sigmatropic rearrangement of 3-allyloxy-1,2,4-oxadiazoles was developed and an insight on the reaction mechanism was gained by analyzing the regio- and stereoselectivity of the reaction. From a synthetic point of view, the proposed rearrangement represents a new entry for the obtainment of N-substituted 1,2,4-oxadiazolones, structurally related to quisqualic acid, as valuable synthons of pharmaceutical interest.

Acknowledgments

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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.2010.12.058.

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14. *Typical experimental procedure for the rearrangement reaction*: 5.6 mg (0.025 mmol) of $Pd(OAc)_2$ and 336 mg (2.5 mmol) of $CuCl_2$ and 0.5 mmol of the allylic substrate were solubilized in dry THF (15 mL) under Ar and stirred for 12 h at 50 °C. The resulting dark green solution was reduced to a little volume by rotavapor. Then 10 mL of water were added and the aqueous phase was extracted with EtOAc. The organic phase was washed with water and brine and dried onto Na_2SO_4. The product was purified by flash chromatography (Si gel Lichroprep® 15–25, 25–40 1:1; elution with light petroleum ether/EtOAc from 50:1 to 5:1).
Compounds **1a–c** are reported in Ref. 15. Characterization data of new compounds (**1d–g**, **2a–g**) are available in the Supplementary data.
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