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Palladium-catalyzed cyclization/allylation of in situ-generated α-hydroxy-[3]-cumulene samarium alkoxides: synthesis of allylated furans

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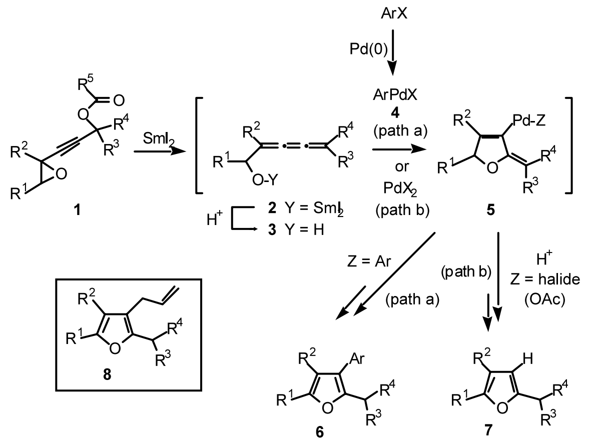
Abstract—Samarium alkoxides of α-hydroxy-[3]-cumulenes, generated in situ by SmI_2-promoted reduction of appropriate epoxypropargyl esters, are found to participate in novel Pd-catalyzed cyclization/allylation sequences in the presence of allylic bromides. This results in the efficient regioselective formation of polysubstituted furans incorporating the allyl unit. © 2003 Elsevier Science Ltd. All rights reserved.

1. Introduction

The palladium-catalyzed sequential cyclization/coupling of alkynes and allenes containing a proximal *C*-, *O*- or *N*-based nucleophile with organic halides or triflates (R–X) is a well established strategy that has led very successfully to the efficient preparation of a variety of substituted carbocyclic and heterocyclic structures incorporating the organic fragment (R).[1]

In recent years this general strategy has attracted much attention in the field of regioselective synthesis of polysubstituted furan and related derivatives from acyclic precursors.[2] This is hardly surprising in view of the interest aroused by these compounds because of their synthetic, biological and industrial relevance.[3] Accordingly, these compounds have been prepared from a variety of alkyne and allene substrates containing a nucleophilic oxygen-based functionality using Pd-catalyzed cyclization/coupling sequences. While aryl- and vinyl halides or triflates have been extensively used in these reactions,[4–16] in comparison, the conceptually similar allylation using allylic halides or equivalent reagents is significantly less represented in the literature.[17–22] This last type of reaction is interesting because it provides eventually, after proper functionalization, a possibility for regioselective introduction of alkyl groups onto the heterocyclic ring. This would be a difficult task if alkylpalladium complexes derived from alkyl halides were to be used directly because of the well known reluctance of alkyl halides to undergo oxidative addition and the tendency of alkylpalladiums to undergo fast β-hydride elimination.[23]

Our own efforts in this area have resulted in the development of a new regioselective route to polysubstituted arylated furans **6** from in situ-generated [3]-cumulene alcohols **3** and aryl halides ArX.[12] In this novel process the arylpalladium complex **4**, generated from ArX and a Pd(0) catalyst, is thought to activate the central C–C double bond of the triene system to nucleophilic attack by the internal hydroxyl group resulting in an alkenylarylpalladium intermediate **5**



Scheme 1.

Keywords: furans; intramolecular oxypalladation; allylation; [3]-cumulenes.

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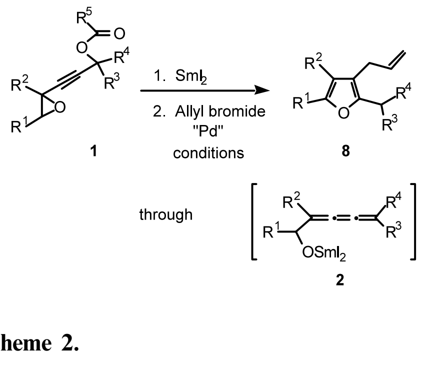
(Z = Ar, path a) that then undergoes reductive elimination and aromatization to yield the observed arylated furan products **6** (Scheme 1).

We have also shown that using instead a Pd(II) catalyst PdX_2, in the absence of an aryl halide, the reaction similarly proceeds to a related alkenylpalladium complex **5** (Z = halide or OAc, path b) to eventually furnish 4-unsubstituted furans **7** via protodemetallation of **5**.[24]

By either mechanism, this kind of reaction appears to be well suited for the preparation of the corresponding allylated furans **8** if allylic halides were used in place of an aryl halide. Thus, furans **8** could evolve by reductive elimination of a (π-allyl)palladium complex of type **5** (Z = allyl) as well as by allylation of the related intermediates **5** (Z = halide or OAc) depending on the catalyst (Pd^0 or Pd^{II}, respectively) being used. This paper reports our preliminary results in this area, resulting in a new synthesis of allylated furans **8** and further developing the use of [3]-cumulene alcohol derivatives as new substrates for Pd-catalyzed sequential heterocyclization/C–C bond formation, a field virtually unexplored so far.[12]

2. Results and discussion

[3]-Cumulene alcohols **3** are easily accessed as diastereomeric mixtures by SmI_2-promoted reduction–elimination of epoxypropargyl esters **1** followed by aqueous work-up.[24,25] However, for the purpose of furan synthesis these key intermediates are best used without isolation or purification either in THF or DMF solvents.[12,24] According to the mechanisms proposed in Scheme 1, and unlike the case of **7**, that obviously requires a source of protons to complete the catalytic cycle, formation of **6** and **8** could take place in the absence of added protons. However, as we have previously reported, the use of aryl halides required in fact the in situ generation of alcohols **3** in order to obtain good yields of **6** (Scheme 1).[12] In striking contrast with this behavior, it is now found that the corresponding allylations to yield **8** work well directly from the samarium alkoxides **2** and that generation of the alcohols **3** is neither necessary nor does it lead to any improvement in the yield of **8**. Therefore, all cyclizations/allylations described here have been conveniently carried out from in situ-generated alkoxides **2** in the absence of an added proton source (Scheme 2).



Scheme 2.

Reaction conditions were selected, after a brief survey, based on previous experience in furan formation from alcohols **3**[12,24] and on related allylations described in the literature.[21] Thus, two sets of conditions have been found to work well in the formation of 3- or 4-allylfurans. Method A is based on a Pd(0) catalyst, $Pd(PPh_3)_4$ (10 mol%), in combination with allyl bromide (10 equiv.) as allylating agent, K_2CO_3 (5 equiv.) and dimethyloxirane (4 equiv.) in DMF. Method B differs from A only in the use of $PdCl_2(MeCN)_2$, a Pd(II) complex, instead of $Pd(PPh_3)_4$. Results using these two conditions with a representative group of substrates **1** are collected in Table 1. As shown there, for all substrates the desired allylated furans **8** were obtained in moderate to good yields under at least one set of conditions.

Some interesting features emerge from these results. For example, while the use of a Pd(0) catalyst gave in most cases comparable or even higher yields than those obtained with Pd(II), higher temperatures were always required to promote the reaction with the former catalyst and the formation of furans **7** was always an undesired side-reaction in those cases. The formation of **7** in these reactions appears to be the result of protonation competing with the desired reductive elimination at the level of an intermediate of type **5** (Z = allyl, Scheme 1). At this point, it is not clear where the required protons come from under the anhydrous conditions utilized all throughout the experimental process, but in this regard it should be noted that the use of both K_2CO_3 and dimethyloxirane has proven crucial to minimize the formation of **7** relative to **8** as well as to provide good yields of products.[26]

As for the scope of the reaction, Table 1 include substrates with acid- or base-sensitive functional groups (**1a**,**c**,**f**,**g**) all of which are well tolerated under Pd(II) conditions. The Pd(0)-catalyzed reaction gave poor results with the OMOM-substituted substrate **1f** for reasons not understood at the moment since the same substrate undergoes the related arylation reaction efficiently with the same catalyst.[25] Conversely, only Pd(0) was capable of promoting the cyclization of the terminal epoxide **1h**, albeit in a moderate yield. The sequence is also useful for formation of bicyclic products, as exemplified with the use of **1c**, and allows α-branching at alkyl substituents in several positions (substrates **1a**,**c**,**e**,**f**). However, a substrate lacking a C(5) substituent (furan numbering) gave a poorer overall result with both catalysts. Therefore, the method appears to be particularly well suited for the preparation of tetrasubstituted furans with complete regioselectivity.

The possibility of extension of this chemistry to other allylic substrates was explored with epoxide **1a** and 3-bromo-2-methylpropene (Scheme 3). In this case, Pd(0) gave the best result, with a rather useful 52% yield of product **9** while Pd(II) afforded a substantially lower yield. The failure of Pd(II) to promote efficiently the reaction in this case is consistent with a reaction pathway for this catalyst that leads to **8** or **9** through an

Table 1. Synthesis of allylated furans **8** from esters **1** and allyl bromide[a]

1	R^1	R^2	R^3	R^4	Catalyst	T (t)[b]	Yield of **8**[c]	Yield of **7**[c]
1a[d]	CH_3	CH_3	$(CH_2)_3CN$	CH_3	$Pd(PPh_3)_4$	60 (24)	49	12
1a[d]	CH_3	CH_3	$(CH_2)_3CN$	CH_3	$PdCl_2(MeCN)_2$	35 (24)	58	0
1b[d]	CH_3	CH_3	$(CH_2)_2Ph$	H	$Pd(PPh_3)_4$	60 (15)	60	9
1b[d]	CH_3	CH_3	$(CH_2)_2Ph$	H	$PdCl_2(MeCN)_2$	35 (16)	52	0
1c[e]	$(CH_2)_4$		$(CH_2)_3CN$	CH_3	$Pd(PPh_3)_4$	60 (24)	63	12
1c[e]	$(CH_2)_4$		$(CH_2)_3CN$	CH_3	$PdCl_2(MeCN)_2$	25 (24)	63	0
1d[e]	$(CH_2)_4$		$(CH_2)_2Ph$	H	$Pd(PPh_3)_4$	50 (15)	65	10
1d[e]	$(CH_2)_4$		$(CH_2)_2Ph$	H	$PdCl_2(MeCN)_2$	35 (16)	58	0
1e[d]	*i*-Pr	*i*-Bu	$(CH_2)_2Ar$[f]	H	$PdCl_2(MeCN)_2$	35 (14)	70	0
1f[d]	CH_2OMOM	CH_3	$(CH_2)_3CN$	CH_3	$Pd(PPh_3)_4$	50 (72)	26	23
1f[d]	CH_2OMOM	CH_3	$(CH_2)_3CN$	CH_3	$PdCl_2(MeCN)_2$	35 (15)	73	0
1g[d]	CH_2OMOM	CH_3	$(CH_2)_2Ph$	H	$PdCl_2(MeCN)_2$	35 (14)	69	0
1h[e]	H	CH_3	$(CH_2)_2Ph$	H	$Pd(PPh_3)_4$	70 (19)	42	0
1h[e]	H	CH_3	$(CH_2)_2Ph$	H	$PdCl_2(MeCN)_2$	35 (17)	[g]	[g]

[a] Experimental procedure: In a typical experiment, to a solution of SmI_2 (ca. 0.1 M, 1.50 mmol) in THF (15 mL) was added via cannula a solution of **1** (0.70 mmol) in THF (2 mL) at −5°C under Ar. The mixture was stirred at the same temperature for 1–5 h (until disappearance of the starting ester as judged by TLC). Dry air (~15 s) and Ar (~10 min) were successively bubbled through the solution, and the reaction mixture was allowed to reach rt. Removal of the solvent in vacuo afforded a residue that was dissolved in DMF (10 mL). To the resulting solution were added K_2CO_3 (0.480 g, 3.50 mmol), allyl bromide (6.99 mmol), 2,2-dimethyloxirane (0.25 mL, 2.80 mmol) and finally $Pd(PPh_3)_4$ (0.080 g, 0.07 mmol) (Method A) or $PdCl_2(MeCN)_2$ (0.020 g, 0.07 mmol) (Method B). The solution was stirred under the conditions of temperature and time indicated in Table 1. Aqueous work-up and purification by liquid chromatography afforded furans **8** and **7**.

[b] Temperature (°C, oil bath) and within parenthesis reaction time (h) for the cyclization/allylation step $\mathbf{2}\rightarrow\mathbf{8}$.

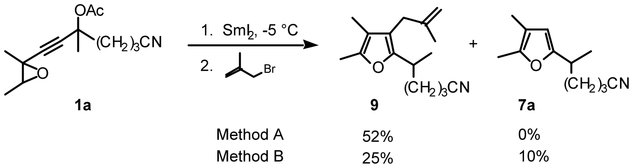
[c] Yield (%) of isolated pure product. All products were characterized by their spectral (^1H and ^{13}C NMR, IR) properties and HRMS.

[d] $R^5=CH_3$.

[e] $R^5=Ph$.

[f] Ar = 3,4-dimethoxyphenyl.

[g] Uncharacterizable mixture of products.



Scheme 3.

intermediate of type **5** (Z = halide or OAc, Scheme 1) via complexation with the alkene double bond, followed by regioselective carbopalladation and PdBrCl elimination.[22,27] A slower carbopalladation due to steric effects[28] and an increased opportunity for β-H elimination competing with the desired β-hetereoatom elimination in a putative intermediate β-bromoalkylpalladium complex[29] could then account for the diminished yield observed in the formation of **9** under these particular conditions. The reactions utilizing $Pd(PPh_3)_4$, on the other hand, should proceed through a (π-allyl)-palladium intermediate of type **5** (Z = allyl, Scheme 1) and be much less sensitive to the above-mentioned effects. Further work with other substituted allylating agents should prove interesting to clarify these mechanistic issues as well as to expand the scope of this methodology.

In summary, polysubstituted furans incorporating an allyl unit are efficiently formed in a one-pot two-step protocol that comprises a SmI_2-promoted reduction of epoxypropargyl esters **1** followed by a Pd-catalyzed cyclization/allylation sequence of the so formed intermediate samarium alkoxide **2** with allylic bromides. The possibility of choosing between two sets of reaction conditions, as well as the use of substrates **1** which are easily assembled from simple building blocks,[24] gives added versatility to the method. This strategy is particularly effective for the regioselective preparation of a novel set of tetrasubstituted furans, compounds for which the literature suffers from a scarcity of regioselective synthetic methods.[12,30] Finally, this work further demonstrates the synthetic utility of α-hydroxy-[3]-cumulenes as new substrates for palladium-catalyzed sequential heterocyclization/C–C bond formation.

Acknowledgements

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