Intramolecular azavinyl carbene-triggered rearrangement of furans†

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An intramolecular rhodium-catalyzed reaction of 1-tosyl-1,2,3-triazoles with furans has been explored. The tosylmino functionality was found to play a significant chemical role participating in the subsequent domino-transformations of a key reaction intermediate. One of the reaction pathways leads to valuable 2-formyl- and 2-acetylpyridine building blocks, which could be obtained in one-pot starting from easily accessible (furan-2-yl)methyl)propargyl amines. An original method for the synthesis of highly functionalized indolizines from the obtained pyridines has been proposed.

Introduction

Ten years ago Gevorgyan and Fokin realized the colossal synthetic potential of metal-intercepted diazoimine tautomers1 of sulfonyl triazoles,2 which were easily accessed through copper-catalyzed azide–alkyne cycloaddition (CuAAC).3 The resulting z-iminocarbenoid species possess the characteristic reactivity of carbenes generated by denitrogenative decomposition of conventional diazo compounds; specifically, they undergo cheletropic reactions, X–H and C–X insertions, ylide formation or rearrangements (Fig. 1).4 However, the sulfonyl imine functionality exhibits untypical nucleophilicity, which allows the azavinyl carbeneoids to undergo transannulations following the addition of a nucleophile to the carbene centre.5 Eventually, such an upgraded reactivity of rhodium transient azavinyl carbeneoid species affords a high level of synthetic flexibility that is to some extent controlled by the nature of a reaction partner.

Furans represent nontrivial biomass-derived building-blocks6 known for their propensity to undergo dearomatization7a forming diverse carbocyclic and heterocyclic8 compounds under electrophilic conditions.

Understandably, furans were tested as nucleophiles in a reaction with carbenes derived from diazo compounds. While intermolecular reactions usually result in the formation of cyclopropane and dienone mixtures with poor regiocontrol,9 intramolecular processes afford better chemoselectivity. In particular, the denitrogenative decomposition of various (furan-2-yl)-tethered diazo compounds usually proceeds through the same spiro-intermediate,10,11 and yet leads to products with limited synthetic utility (Fig. 2a). In turn, decomposition of (furan-2-yl)-tethered 1-sulfonyl-1,2,3-triazoles would result in the formation of a common spiro-key intermediate that could be intercepted by an imino group, leading to compounds of type A (Fig. 2b, path I). Alternatively, the key intermediate might rearrange to azatriene B that could further be converted to a variety of nitrogen-containing heterocycles (Fig. 2b, path II). In either scenario there is the possibility for rapid accessing the molecular complexity from rather structurally simple starting materials.

To our surprise, we could not find any reports on intramolecular rearrangements of furans initiated by iminocarbene species derived from triazoles, although examples of denitrogenative decomposition of triazoles in the presence of a furanyl substituent within the same molecule are known.14,15 In order to fill the methodological gap, we sought to explore the synthetic prospects of the aforementioned transformation. Very
recently, Hashmi et al. described a synthetic method toward functionalized pyrroles based on the rearrangement of a furan ring in the gold(III)-catalyzed reaction of propargylfurufuryl amines with anthranyls. The reaction is believed to proceed through the intermediate formation of gold-stabilized imino-carbene species that attack the furan system followed by its dearomatization. The denitrogenative decomposition of furyl-tethered triazoles, in contrast, would provide regioisomeric iminocarbenes, which upon reaction with a furan ring could lead to the formation of valuable products of different architectures. Herein, we report our initial studies of intramolecular azavinyl carbene-triggered rearrangement of furans.

Results and discussion

Our exploratory studies commenced with triazole 2 as a model substrate, which was obtained via CuAAC from propargyl amine 1a (Scheme 1). Treatment of triazole 2 with rhodium acetate dimer in chloroform at 50 °C led to a full conversion of the starting material within 5 h. Careful analysis of the crude reaction mixture revealed that the main component among the formed products appeared to be dihydropyridine 3. However, all attempts to isolate compound 3 by column chromatography on silica gel failed; the only product detected was 2-acetylpyridine 4a. The same outcome was observed when the reaction mixture was treated with a base. Apparently, the formation of 2-acetylpyridine 4a resulted from 6π-azaelectrocyclization of initially formed dihydropyrrole II followed by aromatization through elimination of sulfinate.

Stimulated by the high synthetic value of 2-acylpyridines as intermediates in medicinal and material chemistry, we decided to study the discovered transformation in more detail. The optimization of reaction conditions revealed that toluene was the solvent of choice for the formation of dihydropyridine 3a (Table 1, entry 1; for more details, see the ESI†). Further screening of rhodium(II) sources led us to identify Rh₂(OOct)₄ as the optimal catalyst for the first cascade transformation (entries 2–5). As compound 3 appeared to be quite unstable, we continued tuning the reaction conditions towards final acetylpyridine 4a in a one-pot mode.

After some experiments, we found that addition of two equivalents of Et₃N resulted in the clean transformation of dihydropyridine 3a into its unsaturated derivative 4a (entry 8).

Fig. 2 Intramolecular rhodium carbenoid-triggered ring-opening of furans: (a) known reactivity; (b) concept for this work.
With the aim of establishing a convenient synthetic method towards 2-acylpyridines, we integrated the CuAAC step into a single one-pot protocol starting from propargyl amines 1. To our delight, the addition of an extra step had almost no effect on the outcome of the model reaction; the yield of pyridine 4a was 88% (Scheme 2). Moreover, on a gram-scale the method afforded pyridine 4a in comparable yield with the use of only 0.5 mol% of rhodium catalyst (see the ESI† for details).

Following the optimization studies, we sought to study the influence of various substituents at different positions of the starting material on the reaction outcome. Substituted propargyl amines 1a-i were screened first (Table 2). Bromo and nitro substituents in other tested sulfonyl protection groups were tolerated well under the optimized conditions (compounds 4b and e). It was possible to introduce substituents at propargylic (compounds 4d and e) and furfuryl positions (compound 4g) of the starting material, although the overall transformation resulted in lower yields of the respective products, probably due to steric reasons. Indeed, more bulky substituents at either position prevented the furan from being attacked by a carbene centre in an initial step: in the cases of starting materials 1f and 1h we observed the formation of corresponding triazoles that decomposed over time. After additional tuning of reaction parameters, we were also able to obtain 2-formylpyridine 4i in 63% yield.

Next, we studied substrates with an extended tether that linked the triazole fragment and a furan ring. Thus, homopropargylamine 5 reacted smoothly under slightly altered reaction conditions to provide tetrahydronaphthiridine 6 (78%) (Scheme 3).

When we tested homofurfurylamine 7, which was forced to react under quite harsh conditions, we observed the formation of pyrrole 8 as well as dihydropropyridine 9 (Scheme 4). Presumably, pyrrole 8 was the product of an alternative reaction where initially formed spiro-intermediate III was trapped intermolecularly with the imino group followed by base-induced ring-opening of dihydrofuran intermediate V (route a). In turn, dihydropropyridine 9 was formed via 6π-azaelectrocyclization of azatriene IV following the ring-opening of initial intermediate III (route b). Evidently, the nature of the tether modulates the geometry of an intermediate III at such an elevated reaction temperature, so that it can demonstrate alternative reactivity.

Dihydropropyridine 9 was found to be more stable than its analogue, dihydropropyridine 3. Conversion of compound 9 into the corresponding pyridine 10 required much harsher reaction conditions as well (Scheme 5).

We examined the reactivity of propargyl ethers 11 that were found to be more reactive than related amines 1 (Table 3).
Consequently, they had to be converted under milder conditions in order to avoid undesired side reactions. Generally, substrates 11 afforded corresponding products 12 in higher yields, even those bearing bulky substituents in the furfuryl position (products 12c and d). Noteworthily, 2-formylpyridine 12e was as well obtained in practical yield.

The reaction of propargyl ethers with voluminous substituents at C(5) of a furan ring (compounds 11f and g) stopped at the formation of Z-azatrienes 13a and b, the products of the ring-opening of the initial spiro-intermediates (Scheme 6). Likely, bulky groups obstruct the electrocyclization of the respective azatrienes. All attempts to force the reactions only led to Z-to-E isomerization of the α,β-unsaturated ketone moiety.

Finally, we probed propargyl ester 14 with a lengthened linker. Under various conditions the only product we always detected was the very unstable enol ether 15, which, apparently, was formed through 1,2-shift of a hydride to a carbene atom. Eventually, we found conditions that provided a nearly quantitative yield of compound 15 (Scheme 7).

It is known that 1,2-hydride shifts often follow the denitrogenative decomposition of 4-alkyltriazoles, which reduces the yields of the target compounds. Possibly, this competing reaction also affects the outcome of the studied processes. It seems that the observed sigmatropic rearrangement is a kinetically controlled reaction in the case of substrate 14: both the longer tether and higher proclivity of the oxygen atom to donate its electron pair (compared to the NTs group) make enol 15 a predominant product.

2-Acylpyridines are known to be largely used for the synthesis of indolizines, indolizidines and their close structural analogues, which represent core frameworks for the vast number of alkaloids and biologically active compounds. We attempted to further extend the application of the obtained

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**Scheme 4** Divergent reactivity of homofurfurylamine 7.

**Scheme 5** Synthesis of tetrahydronaphththridine 10.

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**Scheme 6** Reactivity of propargyl ethers 11f and g.
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Conflicts of interest

There are no conflicts to declare.
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