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Investigation of cationic Claisen-type electrophilic rearrangements of amides

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Dedicated with respect and admiration to Professor Barry M. Trost on the occasion of the Tetrahedron Prize for Creativity in Organic Chemistry 2014

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ABSTRACT

Herein we report an extension of the electrophilic rearrangement of amides to the preparation of α-prenyl-hydrocoumarins, indoles, isoquinolines and dihydro-isoquinolinones. An unusual competitive sulfonyl migration, uncovered upon attempted aza-Claisen rearrangement, is also described.

1. Introduction

The Claisen and related rearrangements are well-established tools in organic synthesis.[1] Our group has reported a 'Claisen-like' intramolecular rearrangement of keteniminium salts, opening a direct and stereoselective route towards challenging substituted lactones.[2] As depicted in Scheme 1a, this process converts simple ω-allyloxy, -propargyloxy and benzyloxyamides into α-substituted lactones in the presence of triflic anhydride (Tf_2O) and 2,4,6-collidine.[2a,3] The formation of the intermediate iminium ether **1a** (Scheme 1a) has been confirmed and lends support to the original mechanistic proposal, involving an intramolecular cyclization followed by a [3,3] sigmatropic rearrangement.[4] Furthermore, incorporation of a phenyl ring within the alkyl tether restricted the conformational freedom and facilitated the cyclization/rearrangement of amide **2** (Scheme 1b).[5]

These results encouraged us to explore these reactions further and, eventually, to develop an aza-Claisen variant, by replacing the oxygen tethering element with a nitrogen atom. In particular, we hoped that this might open a new platform to assemble heterocyclic compounds (Scheme 1c), a valuable endeavour for synthesis, medicinal chemistry and materials science.[6,7]

2. Results and discussion

The recently reported methodology for the preparation of α-substituted lactones via a [3,3] sigmatropic rearrangement, involving the formation of a keteniminium ion intermediate, presents several advantages: high accessibility of starting materials; relatively high yields; broad substrate scope and simple reaction conditions. This procedure was applied for the preparation of α-prenyl hydrocoumarin derivatives, useful as substrates in organocatalytic transformations.[8] Thus, in our initial studies, we attempted to prepare five-membered ring substrates by applying the rearrangement conditions (Tf_2O, collidine, 120 °C, 5 min) to the readily available *o*-allyl phenol **4**. Indeed, the rearrangement intermediate

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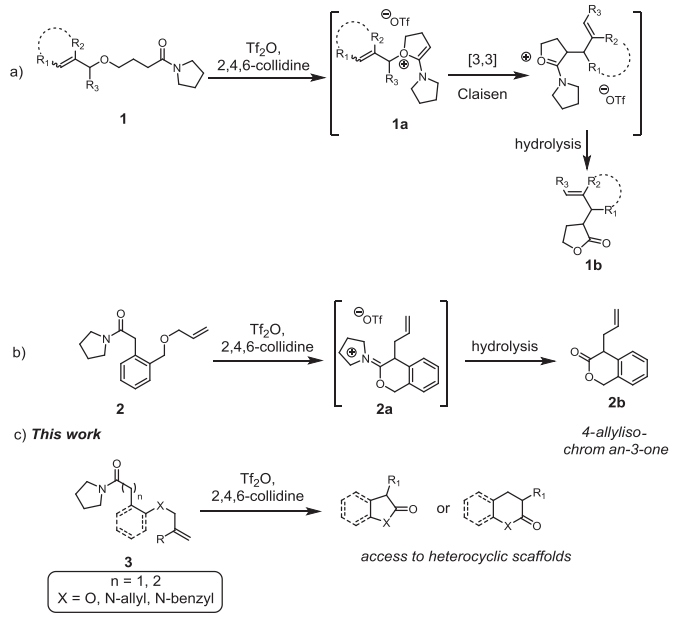
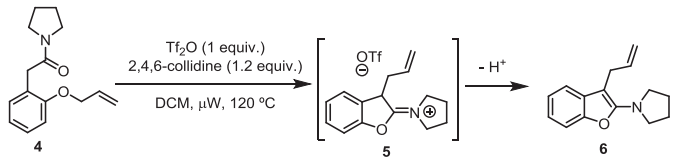


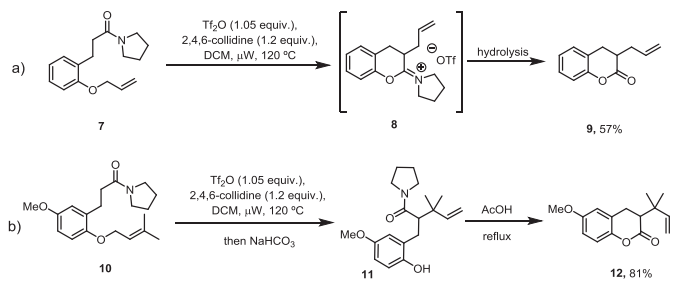
Scheme 1. Preparation of lactones and ring-fused heterocycles by a Claisen-like rearrangement via formation of iminium ether intermediates.

5 was detected by NMR of the reaction mixture (Scheme 2). However, efforts to hydrolyse the intermediate **5** proved fruitless, as the 2-aminobenzofuran **6** resulted as the only observable product.



Scheme 2. Rearrangement of **4** to a benzofuran derivative **6**.

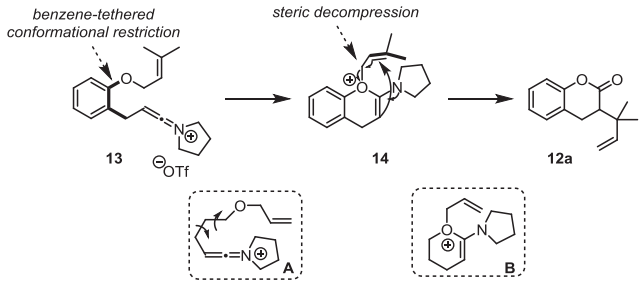
Acknowledging that the aromaticity of benzofuran **6** was behind our inability to hydrolise **6**, we turned towards substrate **7**, obtained from commercially available α,β-unsaturated coumarin. It is worth noting here that hydrocoumarins, also known as flavanoids, show vast biological activity.[9] Although a simple alkylation can provide derivatization on α-position, sterically hindered alkyl and aryl substituents cannot readily be introduced via alkylation. Recognizing the facile reactivity shown above, we presumed that hydrocoumarin-derived substrates would be capable candidates for the rearrangement reaction. After simple preparation of substrate **7**, subsequent rearrangement provided α-allylated compound **9** upon hydrolysis in moderate yield (Scheme 3a).



Scheme 3. Rearrangement of substrates **7** and **10**.

We thus decided to probe this methodology for the synthesis of α-reverse prenylated hydrocoumarin derivatives (Scheme 3b). Reverse prenylation is typically a challenging transformation and [3,3] sigmatropic rearrangement of a 'normal' prenyl substrate such as **10**, whenever possible, offers a straightforward alternative.[10] Under the standard rearrangement conditions, **10** was completely consumed to a new product after hydrolytic work-up. NMR analysis revealed that this was in fact the ring-opened amide **11** (in a mixture with collidine). After a survey of different conditions, we found that exposure to boiling acetic acid led to the hydrocoumarin **12** in 81% yield.

It should be noted that, in our original study of this transformation (Scheme 1a),[1a] reverse prenylation was not possible. Thus, the success observed in the transformations of Scheme 3 is worthy of note. As depicted in Scheme 4, it is likely that the presence of the aromatic ring in **13** facilitates the nucleophilic attack of the oxygen atom, placing it in closer proximity to the keteniminium ion when compared to the aliphatic chain **A** (represented in the box) (Scheme 4). Furthermore, steric decompression during the rearrangement event (compare **14** with **B**) might also account for the reaction outcome.



Scheme 4. Conformational and electronic comparison of rearrangements for acyclic and aromatic substrates.

We then proceeded to examine the reaction scope for the preparation of hydrocoumarins with a series of allyl and alkynyl substrates (Scheme 5).

In spite of the generally moderate yields, all the substrates probed gave the corresponding hydrocoumarins. Substitution at the aromatic ring did not influence the reaction outcome, as well as substitution at the olefinic tether. Compound **16g** was isolated in a lower yield due to concomitant decomposition under the reaction conditions. A propargylated substrate furnished the corresponding hydrocoumarin **16h** possessing an allene group. However, the reaction did not proceed for substrates carrying a substituent at the terminal carbon of the double bond. The observed lower reactivity of these compounds might be due to the additional steric hindrance during the rearrangement step.

At this juncture, we became interested in investigating the aza-variant of this transformation. In this apparently simple replacement of oxygen for nitrogen, substrate design was a concern from the outset, as the reaction was expected to proceed according to the mechanism[2a,3] depicted in Scheme 6. In the aza-substrate an additional substituent is required at the nitrogen atom. Importantly, this substituent must be capable of reducing the nucleophilicity of the *N*-atom while at the same time not competing with the amide for the electrophilic Tf_2O activator (thus excluding amide, carbamate—and related—groups from consideration). The tosyl (Ts) group covers these requirements and it was therefore the substituent of choice.

Our preliminary studies focused on alicyclic amine substrates. The starting materials were prepared in two simple steps. Having