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Rapid Synthesis of Fused Oxabicycles through the Molecular Rearrangement of Spirocyclic Ethers

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Keywords: Rearrangement / Sustainable chemistry / Oxygen heterocycles / Spiro compounds / Ethers

A molecular rearrangement of 5,5-spirocyclic cyclopentenones to 5,6-fused cyclopentenones catalyzed by Amberlyst®15 is described. This work emphasizes the utility of renewable resources, such as furfural, that can be transformed into a variety of valuable products. It also highlights the viability of 5,5-spirocycles as intermediates en route to 5,6-fused cyclopentenones.

Introduction

The majority of industrial chemical processes are based on petrochemical feedstock; limited supplies of crude oil are declining, which has resulted in an ever-gaping need for the development of routes to chemicals, materials, and fuels from renewable resources such as biomass.[1] Materials derived from nonedible renewable resources, ideally byproducts in food production processes, are consequently increasingly valuable starting materials for chemistry. One such raw material, furfural, is produced from hemicellulose derived from agricultural waste products such as bagasse, oat hulls, and corncobs.[2] In today's increasingly globally conscientious society, environmentally benign stock chemicals are important to sustainable development through ensuring a future supply of raw materials.

In the USA, furfural is produced on an estimated scale of 300000 tons annually at a current cost of $366/t.[3] With this considered, it is no surprise that the chemistry of furfural continues to inspire the development of new methodologies[4] that are an asset to a number of research areas.[5] Our recent work on the development of the aza-Piancatelli reaction commenced with the synthesis of furylcarbinols from furfural and their subsequent conversion into 4-aminocyclopentenones, see Figure 1 (a).[6] A natural extension of this work was to investigate the intramolecular reaction to make azaspirocycles [Figure 1 (b) X = ArN] as well as the corresponding intramolecular oxa-Piancatelli reaction to afford oxaspirocycles [Figure 1 (b) X = O].[6b,6c] Over the course of these studies, it became apparent to us that we were in the position to access two valuable products from one sustainable starting material through a molecular rearrangement, see Figure 1 (c).

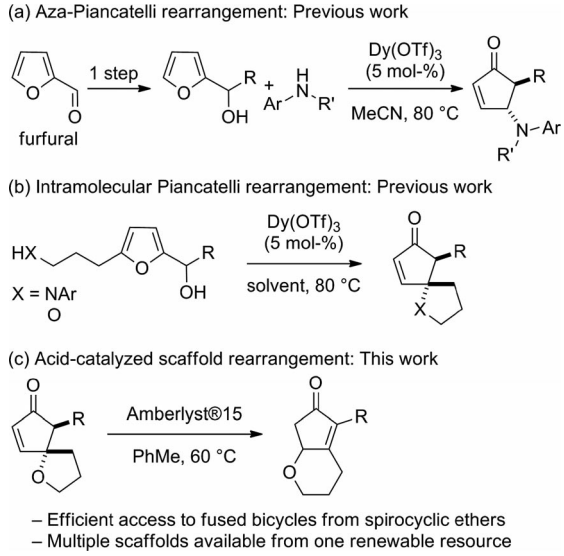

Figure 1. Progress of the Piancatelli reaction.

To date, the isomerization of spirocyclic cyclopentenones to fused cyclopentenones as shown in Figure 1 (c) is unknown. To address this limitation and to provide efficient access to fused oxabicycles, we decided to explore this molecular rearrangement. We were intrigued by this transformation because oxabicycles are an important class of compounds in organic synthesis and they have served as key intermediates in the total synthesis of numerous biologically active molecules. Moreover, reaction design that conscientiously incorporates renewable resources and facile processing to access a different synthetically viable scaffold is critical to the move toward global sustainability on a laboratory scale. Herein, we report the optimization and scope for the formation of oxabicycles **2** from oxaspirocycles **1**, both derived from one common starting material.

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Several procedures have been developed to facilitate the rearrangement of substituted 4-hydroxycyclopentenones, generally en route to prostaglandins (Figure 2).[4b] The migration of the alcohol functional group can occur in an intramolecular fashion (Figure 2, a)[7] or through a hydration–dehydration sequence (Figure 2, b).[8] Wu and coworkers recently took advantage of a two-step sequence, nucleophilic addition of a tethered alcohol followed by elimination of water, to gain access to fused oxabicycles from the corresponding 4-hydroxycyclopentenones (Figure 2, c).[9] We sought to develop a new strategy that would proceed through the spirocyclic ether and upon combination with our previous methodology would offer straightforward access to two classes of oxabicycles from the same furylcarbinol starting material.

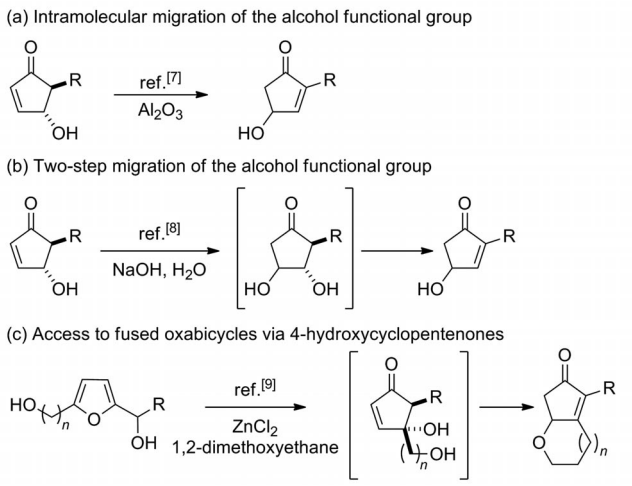
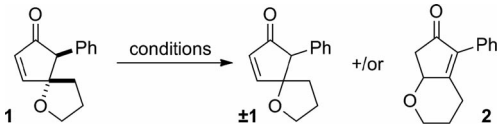


Figure 2. Migration of alcohol functional group.

Results and Discussion

Given the mechanistic possibility that spirocyclic ether **1** could be a precursor to the more thermodynamically stable oxabicyclic cyclopentenone **2**, we decided to further investigate this relationship (Table 1). Initially, we attempted the conversion between the two bicycles by using reaction conditions previously described by Wu et al. ($ZnCl_2$ in refluxing aqueous 1,2-dimethoxyethane).[9] No change to the spirocycle was observed, and **1** was recovered from the reaction in good yield with little to no decomposition. Treatment of the spirocycle with basic alumina resulted in complete erosion of the *trans* selectivity through epimerization; however, no desired rearrangement was observed. Interestingly, other bases such as 4-(dimethylamino)pyridine, Hünig's base, cesium carbonate, sodium carbonate, and sodium phosphates resulted in only recovered starting material. On the basis of these experiments, we further examined the use of other acids (Table 1, entries 3–7), which also resulted in epimerization of the *trans*-substituted spirocycle to a mixture of *trans* and *cis* isomers to varying degrees along with other unidentified minor reaction components. Treatment of **1** with sulfuric acid resulted in its decomposition within minutes. A notable exception was *p*-toluenesulfonic acid, which showed the fused cyclopentenone in roughly 50% conversion after 24 h. We were pleased to find that the acidic ion-exchange resin Amberlyst®15 could be used to carry out the same transformation in a cleaner and more efficient manner; treatment of **1** with acidic Amberlyst®15 provided fused bicycle **2** in excellent yield (Table 1, entry 8).

Table 1. Optimization studies for the scaffold rearrangement.[a]



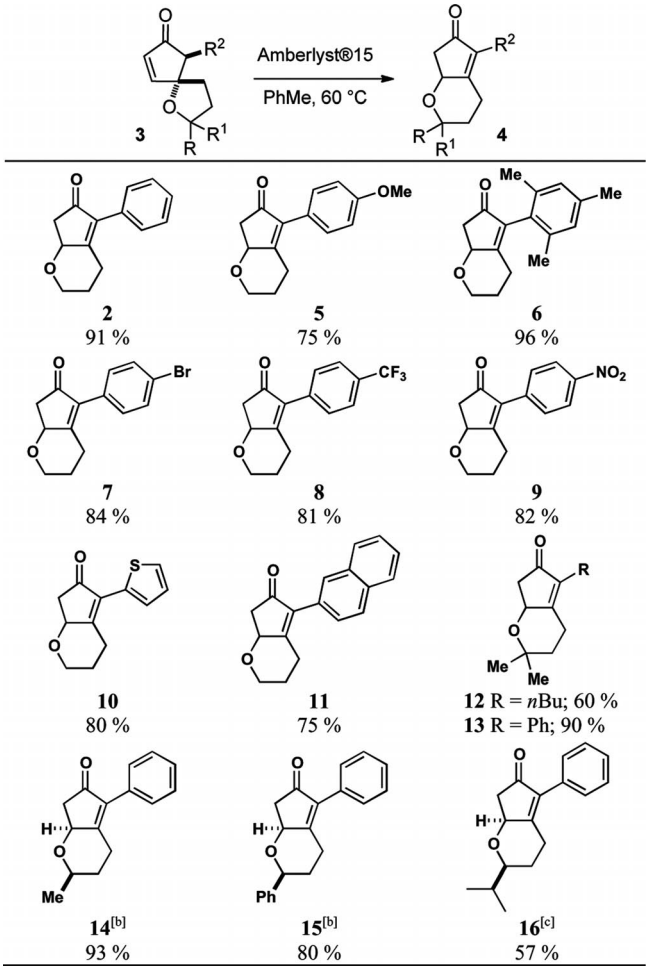
Entry	Reagent (mol-%)[b]	Yield [%] *trans*-**1**/*cis*-**1**/**2**[c]
1	basic alumina (na)[d]	45:45:0
2	$ZnCl_2$ (20)	89:5:0
3	HCl (20)	57:3:0
4	H_2SO_4 (20)	decomposition
5	CSA (20)	66:9:0
6	*p*TSA (20)	41:3:36
7	PMA (20)	45:45:0
8	Amberlyst® 15 (na)[d]	0:0:91

[a] Reactions were performed in toluene at 60 °C. [b] CSA = camphorsulfonic acid, *p*TSA = *p*-toluenesulfonic acid, PMA = polyphosphomolybdic acid. [c] Determined by analysis of the reaction mixture by ^{1}H NMR spectroscopy. [d] n.a.: not applicable.

Importantly, this skeletal rearrangement is general and can be used to efficiently prepare the fused oxabicycles directly from their spirocyclic precursors in high yield (Table 2). All substrates subjected to the reaction conditions behaved accordingly. The rearrangement was extremely clean for electron-rich, electron-poor, and bulky-substituted cyclopentenones (i.e., **5**, **6**, **7**–**9**) but slower and slightly lower yielding if the ether oxygen atom was substituted with a *gem*-dimethyl group (i.e., **12** and **13**). We were thrilled to discover that treatment of a mixture of diastereomers at the γ position of the spirocyclic ether to the reaction conditions resulted in the formation of a single diastereomer of the bicyclic ether (i.e., **14** and **15**). An *anti* relationship, corresponding to the more thermodynamically stable product, was confirmed by NOE experiments.[10] Interestingly, for isopropyl substrate **16**, only a 7:1 ratio was achieved. The molecular rearrangement allowed efficient access to chrycorin (**10**), a natural product with plant growth inhibitor properties, isolated from *Chrysanthemum coranarium* by Tada and Chiba.[9,11] Moreover, the skeletal rearrangement demonstrated that spirocyclic ethers are a viable intermediate in the synthesis of oxabicyclic cyclopentenones from an acid-catalyzed cascade rearrangement of α-furylcarbinols.

From a mechanistic and synthetic point of view, it is interesting that only a single diastereomer was isolated in the case of substituted products **14** and **15** from a 2:1 diastereomeric mixture of the starting materials. It could be considered that the skeletal rearrangement follows a stepwise pathway (Figure 3) that allows the interconversion of intermediates to thermodynamically favored cyclopentenone framework **2**. In acidic media, protonation of

Table 2. Substrate studies for the scaffold rearrangement.[a]



[a] Yield of isolated product. [b] Isolated as a single diastereomer. [c] A 7:1 ratio of diastereomers was obtained.

spirocyclic ether **1** in combination with the acidity of the (here, benzylic) proton in **I** and the proximity of the carbonyl group leads to cleavage of the ether to give alcohol **II**. This extremely reactive species would close rapidly through attack of the primary alcohol to give intermediate **III**, which upon tautomerization yields thermodynamically favored, fused cyclopentenone **2**.

If a secondary alcohol is used, as in the case of products **14** to **16**, a secondary alcohol substituent in the equatorial position during ring closure minimizes unfavorable steric interactions (Figure 3). The possibility of introducing 1,3-diaxial interactions is illustrated clearly in the obtained crystal structure of product **14** (Figure 4).[12]

Notably, we can access the desired fused cyclopentenone framework directly from furfural-derived starting materials (Table 3).[9] Treatment of furylcarbinol **17** with Amberlyst®15 and heating in toluene at 60 °C gave the desired product in 39% yield (Table 3, entry 1). Heating the furylcarbinol at 100 °C followed by treatment with Amberlyst®15 at 60 °C produced the product in only 16% yield. We were surprised to discover that treatment of furylcarbinol **17** with $Dy(OTf)_3$ (Tf = trifluoromethylsulfonyl) and

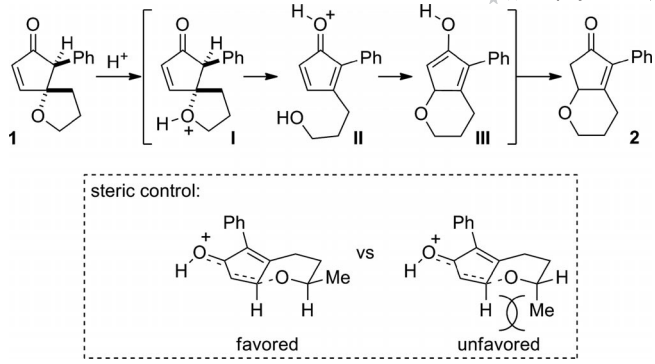


Figure 3. Possible mechanism of the skeletal rearrangement and proposed source of selectivity.

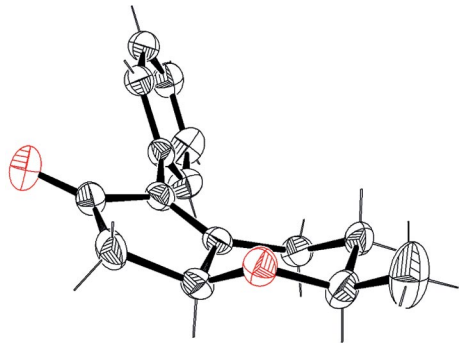
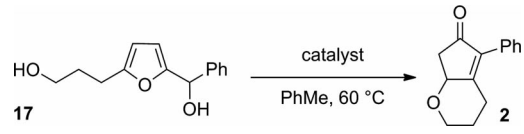


Figure 4. ORTEP structure of fused cyclopentenone **14**. Ellipsoids drawn at 30% probability.

Amberlyst®15 concurrently (Table 3, entry 3) gave fused cyclopentenone **2** in only 34% yield. On the basis of Wu's one-pot protocol in which water was found to be critical to obtain good yields,[9] we tested if water would have a similar effect on the one-pot reaction in Table 3. Unfortunately, the addition of water as a co-solvent (1:1, H_2O/PhMe) gave similar results. During the course of these reactions, spirocyclic ether **1** was observed, along with a number of by-products. These results suggest that our one-pot reactions go through the formation of **1**, which is presumably responsible for the low yields. This is not entirely surprising, because in our previous studies on the formation of **1** from the corresponding furylcarbinol, extensive optimization of the reaction conditions was required to achieve good yields. Although our protocol allows direct access to fused cyclopentenone **2** directly from furylcarbinol **17**, the described

Table 3. Testing a one-pot procedure.



Entry	Catalyst	Yield [%]
1	Amberlyst®15	39
2	100 °C, then Amberlyst®15	16
3	$Dy(OTf)_3$ (5 mol-%) + Amberlyst®15	34

two-step protocol is superior for the conversion of spirocycle **1** into cyclopentenone **2**.

Conclusions

In conclusion, we have demonstrated the operationally simple conversion of spirocyclic ethers into fused bicyclic ethers through an acid-catalyzed isomerization. This transformation provides direct access to fused oxabicycles, which are important intermediates in the total synthesis of numerous biologically active molecules. We believe this approach to fused oxabicycles is attractive, because it demonstrates the versatile nature of using renewable resources to build molecular diversity, and as such, current efforts are focused on extending this methodology to include industrially important transformations and to utilizing our products as substrates for further synthetic manipulations.

Experimental Section

General Procedure for the Synthesis of Fused Bicyclic Ethers: Oxaspirocycle **1** (0.05 mmol) was stirred as a solution in toluene (1.2 mL) at 23 °C and treated with Amberlyst®15 (20 mg). The reaction flask was immediately placed in an oil bath preheated to 60 °C. Upon completion of the reaction (as evident by TLC), the reaction mixture was cooled to room temperature and filtered through cotton and eluted with ethyl acetate. The combined organic layer was concentrated in vacuo to afford oxabicycle **2**.

Supporting Information (see footnote on the first page of this article): General procedures and characterization data of compounds.

Acknowledgments

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[10] On the basis of the NOE and crystal structure of **14**, the stereochemistry of **15** and **16** were assigned by analogy.

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[12] See the Supporting Information. CCDC-931233 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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