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Medium Ring Ethers via [1,2]-Shift of Acetal-Derived Oxonium Ylides

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Abstract: Cyclic acetals and ketals with pendant diazoketones rearranged to O-bridged medium ring ethers in the presence of catalytic $Rh_2(OAc)_4$ or $Cu(hfacac)_2$. This process proceeds via fused bicyclic oxonium ylides which undergo [1,2]-shift reactions. The observation of efficient migration by alkyl substituted carbons lacking any conjugating groups is especially notable. Overall, this chemistry furnishes functionalized medium ring ethers in a few steps from simple precursors. © 1998 Elsevier Science Ltd. All rights reserved.

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Medium sized cyclic ethers are structural motifs found frequently among marine natural products,² and a number of elegant strategies for constructing such systems have been reported.³ An important issue in approaching these targets is the unique difficulties inherent to the formation of medium sized rings.⁴ Our interest in the rearrangement chemistry of oxonium ylides⁵ suggested a possible route. In particular, previous studies had shown that 5- or 6-membered cyclic ethers with pendant diazoketones underwent efficient conversion to oxygen-bridged medium sized carbocycles via fused bicyclic oxonium ylide intermediates.^{5b} Here we report that related ylides derived from readily accessible cyclic acetals or ketals bearing pendant diazoketone groups undergo efficient [1,2]-shift to furnish medium sized ethers bridged by a second ether.⁶

Scheme 1



0040-4039/98/\$19.00 © 1998 Elsevier Science Ltd. All rights reserved. *PII:* S0040-4039(98)00856-9 Preparation of the necessary substrates was straightforward from acetals and ketals $1.^7$ Saponification with K_2CO_3 or LiOOH⁸ (1a/1b and 1d), hydroboration followed by PDC oxidation (1c), or oxidative cleavage⁹ followed by sodium chlorite oxidation of the resulting aldehyde¹⁰ (1e) yielded the necessary acids 2a-e (Scheme 1). Conversion to the acid chlorides and reaction with diazomethane¹¹ efficiently yielded the requisite diazoketones 3a-e. In the case of 5-membered benzylidene acetals 1a/1b, the two diastereomers were carried through the sequence as a 1.3:1 mixture and separated after their conversion to diazoketones 3a/3b.^{7b}

Treatment of **3a-e** with either catalytic $Rh_2(OAc)_4$ or $Cu(hfacac)_2$ led to the corresponding bridged bicyclic ethers **4** in 30-96% yield (Scheme 2).¹² Five-membered benzylidene acetals **3a** and **3b** underwent efficient conversion to a mixture of the diastereometric products **4a** and **4b**, with the product ratios displaying some dependence on catalyst. The structure of **4b** was rigorously determined by x-ray diffraction analysis,⁷ and the stereochemistry of the other products was assigned by spectral analogy. Assuming cis-fused oxonium ylide intermediates (**5a** and **5b**), **4a** would be the expected product of [1,2]-shift with retention from **3a** and **4b** from **3b**. In the event, both $Rh_2(OAc)_4$ and $Cu(hfacac)_2$ furnished **4a** as the major product from **3a**. In contrast, **3b** led to mostly **4a** rather than the expected **4b** with $Rh_2(OAc)_4$, while with Cu(hfacac)_2 there was a slight preference for **4b**. In the case of six-membered benzylidene acetal **3c**, a roughly equal mixture of diastereomeric products **4c** and **4d** was formed regardless of catalyst.

н

5a

н

5b

M



The related five- and six-membered acetonides 3d and 3e were also examined. With $Rh_2(OAc)_4$, 3d furnished roughly equal quantities of the desired [1,2]-shift product 4e and the C-H insertion product 6. This result is not surprising, given the well precedented activation by ethers of neighboring C-H bonds towards Rh-carbenoid insertion.¹³ In addition, the absence of a conjugating group (e.g., phenyl) on the migrating carbon would be expected to raise the barrier for [1,2]-shift by the ylide.¹⁴ If ylide formation is reversible,^{5b,15} other processes such as C-H insertion could become more competitive. Treatment of 3d with Cu(hfacac)₂ gave 4e in high yield to the exclusion of 6. This result is consistent with the previously noted preference for ylide formation over C-H insertion for Cu-carbenoids.^{5e,16} In fact, Cu(hfacac)₂ consistently produced cleaner reactions and higher yields of [1,2]-shift product in all cases. Six-membered acetonide 3e furnished rearrangement product 4f in good to excellent yield with both catalysts. The alternative C-H insertion process would not be expected to compete in this case, as the activated C-H bond is both more distant and sterically encumbered by the neighboring quaternary center.

The lack of stereospecificity observed for 3a-c contrasts with the previously described tetrahydrofuranyl and tetrahydropyranyl examples.^{5b} In each of those cases, the chiral phenyl-substituted center migrated with substantial or complete retention. Formation of mostly 4a from either 3a or 3b demands a stepwise mechanism with a common intermediate, and is consistent with the notion that the carbon-carbon bond-forming step is slow relative to bond rotation in the intermediate. The presence of an oxygen atom adjacent to the migrating center should confer additional stabilization to an intermediate biradical such as 7a,¹⁷ or it may permit the intervention of an alternative heterolytic pathway via ion pair 7b (Scheme 3).¹⁸ The influence of the oxygen is also presumably responsible for the successful rearrangement of acetonide cases 3d,e despite the lack of a conjugating group to stabilize the intermediates. Prior reports by Zercher⁶ and Johnson¹⁹ confirm the ability of an ether oxygen to support efficient [1,2]-shifts by oxonium ylides. However, the complete destruction of unsubstituted acetal 3f with no observation of any of the desired rearrangement product 4g implicates the likely importance of alkyl substitution on the migrating carbon.



Scheme 3

We have shown that simple benzylidene acetals or acetonides bearing pendant diazoketones undergo efficient rearrangement to O-bridged medium-ring ethers via [1,2]-shift of the intermediate oxonium ylides. The ready

availability of the substrates, the excellent yields realized under $Cu(hfacac)_2$ catalysis and its potential use in combination with asymmetric catalysis²⁰ make this an attractive approach to cyclic ethers. Further applications of this methodology will be reported in due course.

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