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LETTERS

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

Richland W. Tester[1] and F. G. West*

Department of Chemistry, University of Utah, 315 S. 1400 East, Rm. Dock, Salt Lake City, UT 84112, USA

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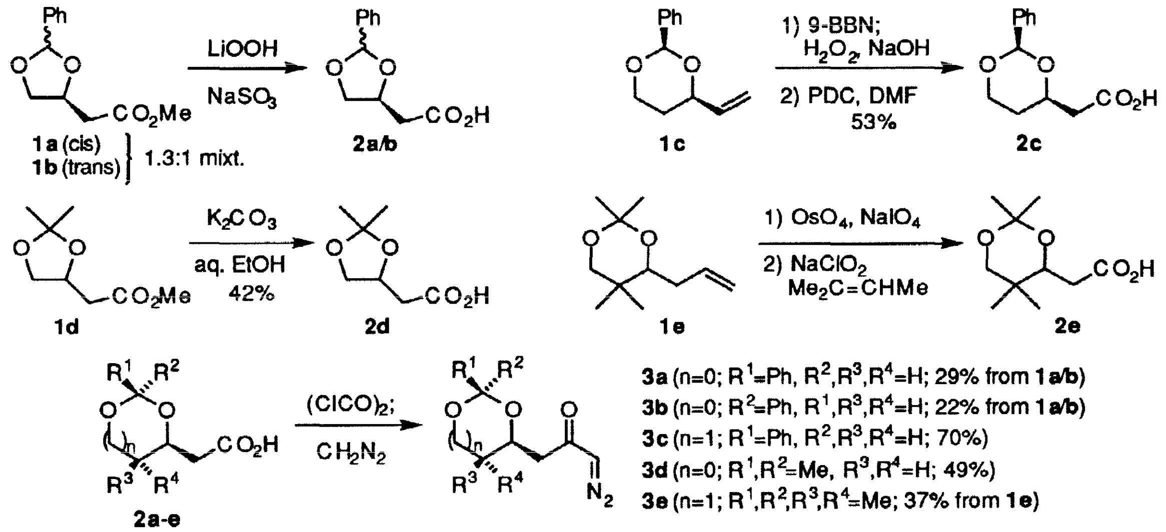
Abstract: Cyclic acetals and ketals with pendant diazoketones rearranged to O-bridged medium ring ethers in the presence of catalytic $Rh_2(OAc)_4$ or $Cu(hfacac)_2$. This process proceeds via fused bicyclic oxonium ylides which undergo [1,2]-shift reactions. The observation of efficient migration by 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.

Keywords: acetals; diazo compounds; medium-ring heterocycles; ylides

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 ylides[5] 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



3a (n=0; R^1=Ph, R^2,R^3,R^4=H; 29% from **1a/b**)
3b (n=0; R^2=Ph, R^1,R^3,R^4=H; 22% from **1a/b**)
3c (n=1; R^1=Ph, R^2,R^3,R^4=H; 70%)
3d (n=0; R^1,R^2=Me, R^3,R^4=H; 49%)
3e (n=1; R^1,R^2,R^3,R^4=Me; 37% from **1e**)

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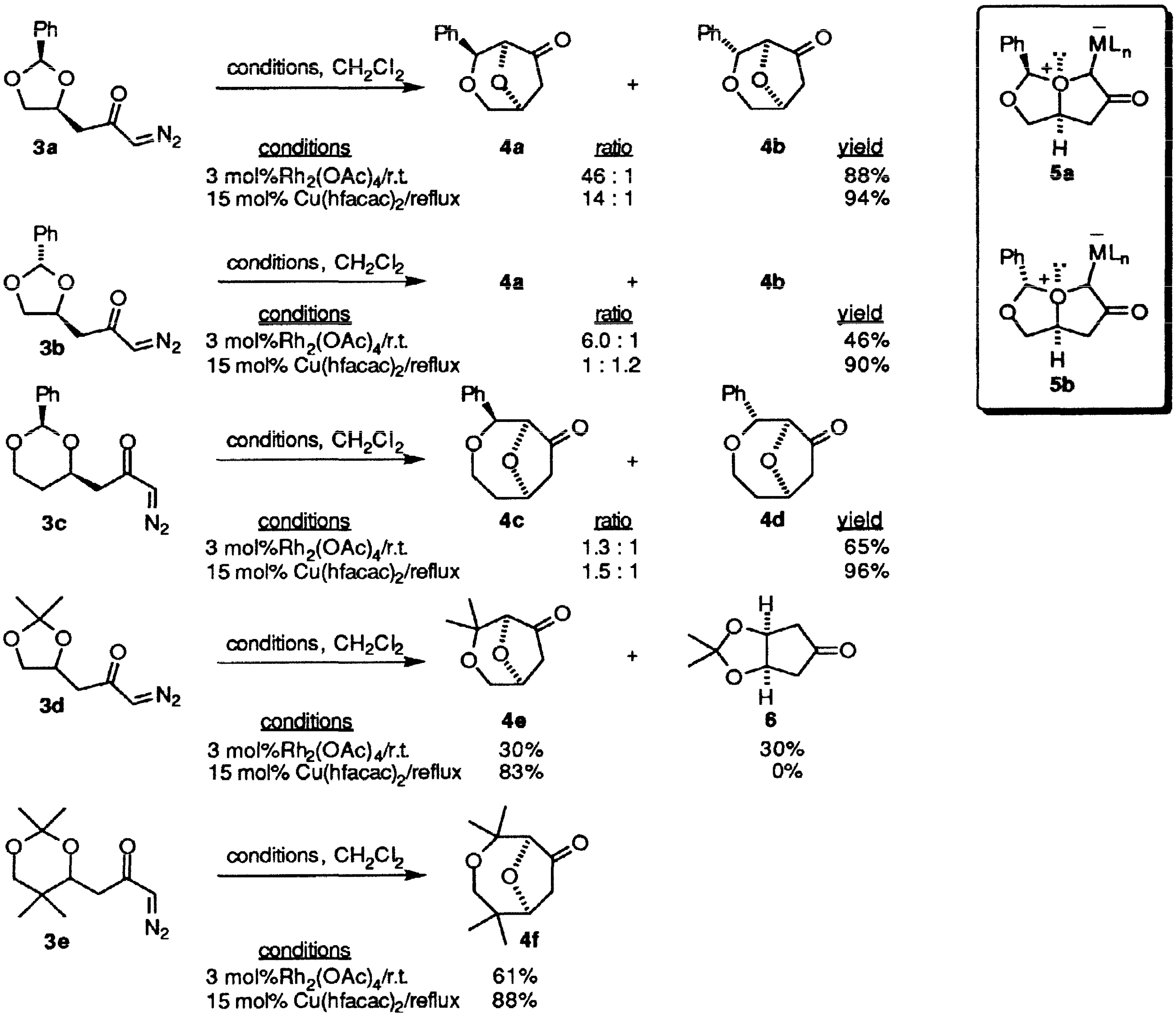
Preparation of the necessary substrates was straightforward from acetals and ketals **1**.[7] Saponification with K_2CO_3 or LiOOH[8] (**1a**/**1b** and **1d**), hydroboration followed by PDC oxidation (**1c**), or oxidative cleavage[9] followed by sodium chlorite oxidation of the resulting aldehyde[10] (**1e**) yielded the necessary acids **2a-e** (Scheme 1). Conversion to the acid chlorides and reaction with diazomethane[11] 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 diastereomeric 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.

Scheme 2



conditions	4a : 4b ratio	yield
3 mol%$Rh_2(OAc)_4$/r.t.	46 : 1	88%
15 mol% $Cu(hfacac)_2$/reflux	14 : 1	94%

conditions	4a : 4b ratio	yield
3 mol%$Rh_2(OAc)_4$/r.t.	6.0 : 1	46%
15 mol% $Cu(hfacac)_2$/reflux	1 : 1.2	90%

conditions	4c : 4d ratio	yield
3 mol%$Rh_2(OAc)_4$/r.t.	1.3 : 1	65%
15 mol% $Cu(hfacac)_2$/reflux	1.5 : 1	96%

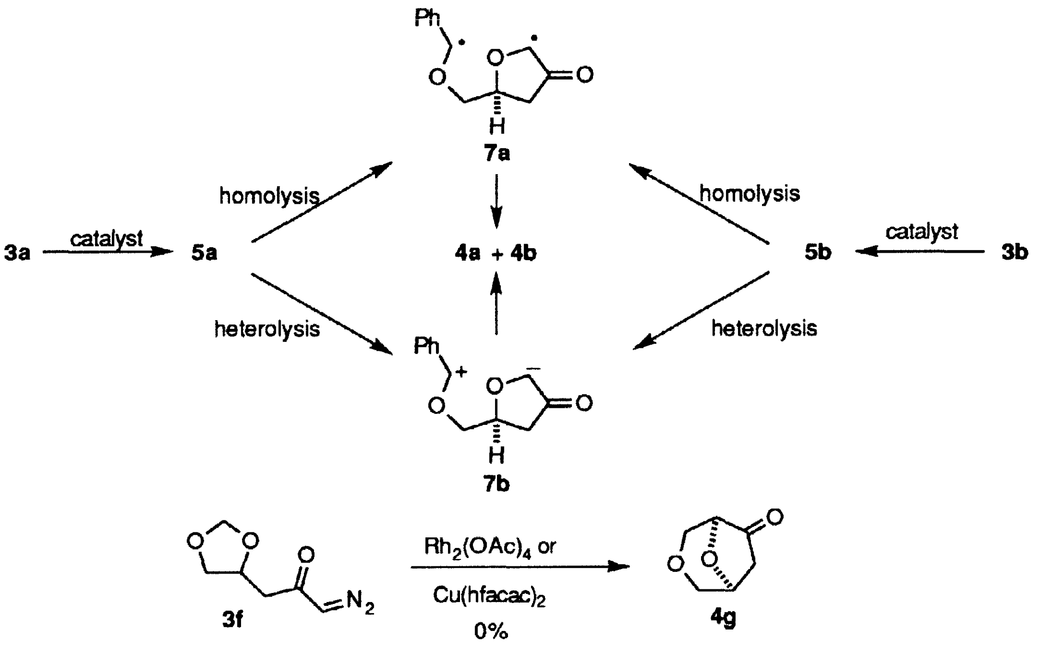
conditions	4e	6
3 mol%$Rh_2(OAc)_4$/r.t.	30%	30%
15 mol% $Cu(hfacac)_2$/reflux	83%	0%

conditions	4f
3 mol%$Rh_2(OAc)_4$/r.t.	61%
15 mol% $Cu(hfacac)_2$/reflux	88%

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.[5c,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 Zercher[6] and Johnson[19] 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 catalysis[20] make this an attractive approach to cyclic ethers. Further applications of this methodology will be reported in due course.

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7. (a) Acetal- or ketal-containing starting materials **1** were readily available from the corresponding diols: Tester, R. W.; Arif, A. M.; West, F. G. manuscript in preparation. (b) The stereochemistry of cis and trans isomers **3a**,**b** was assigned by analogy to related tetrahydrofurans,[5b] and that of **3c** by the known thermodynamic preference for an all equatorial disposition of substituents.
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12. Sample procedure: A solution of acetonide **3d** (75 mg, 0.41 mmol) in CH_2Cl_2 (10 mL) was added to a refluxing solution of Cu(hfacac)$_2$ (30 mg, 0.061 mmol) in CH_2Cl_2 (30 mL) via syringe pump over a period of 1 h. Following the addition, the reaction mixture was stirred at reflux for an additional 0.25 h, then allowed to cool to r.t. A 5% aq. solution of NH_4OH (30 mL) was added, the phases were separated, and the aq. layer was extracted with CH_2Cl_2 (2 x 25 mL). The combined organic layers were washed with sat. NaCl (50 mL), dried ($MgSO_4$) and concentrated to give a greenish oil which was purified by radial chromatography (silica gel, 1 mm plate, hexanes/EtOAc 7:3) to give 53 mg (83%) of **4e** as a colorless oil: R_f 0.21 (hexanes/EtOAc 4:1); IR (neat) 1751 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.55 (br d, J = 7.6 Hz, 1H), 4.22 (dd, J = 11.9, 1.2 Hz, 1H), 3.46 (s, 1H), 3.42 (d, J = 11.9 Hz, 1H), 2.56 (dd, J = 17.7, 7.6 Hz, 1H), 2.31 (d, J = 17.7 Hz, 1H), 1.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.3, 82.3, 74.4, 73.9, 65.0, 38.9, 23.5, 20.4; HRMS calcd for $C_8H_{12}O_3$ *m/e* 156.0801, found *m/e* 156.0795.
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