Communications to the Editor

Reversing the Polarity of Enol Ethers: An Anodic Route to Tetrahydrofuran and Tetrahydropyran Rings

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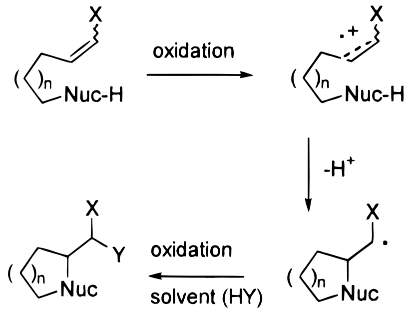
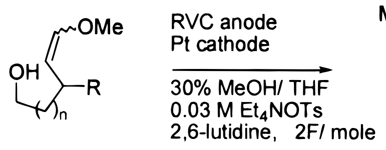
Anodic oxidation reactions have proven to be valuable tools for reversing the polarity of enol ethers and intiating radical cation based oxidative cyclization reactions (Scheme 1).[1] To date, these efforts have focused on the coupling of electron-rich olefins and the formation of carbon−carbon bonds. However, because of the prevalence of tetrahydrofuran and tetrahydropyran rings in biologically relevant natural products,[2] we became interested in determining whether such an approach might also provide a unique pathway to heterocycles (Nuc-H = OH or RNH). While easy to suggest, the compatibility of the reactions with heterocyclic trapping groups was not guaranteed. Efforts to explore the mechanism of the reactions had shown that the addition of an enol ether radical cation to an olefinic nucleophile led to the formation of a radical at the terminating end of the cyclization.[3] For an oxygen-trapping reaction to be successful, the radical cation would need to behave in the opposite fashion. In this paper, we report that enol ether radical cations can be efficiently trapped with alcohols and that the resulting cyclizations can be used to form both tetrahydrofuran and tetrahydropyran rings.

Initially, the cyclization of substrates **1a**−**e** was studied (Scheme 2).[4,5] In each case, the oxidation reaction was accomplished using a reticulated vitreous carbon anode,[6] an undivided cell, a constant current of 8 mA, a platinum auxiliary electrode, a 0.03 M tetraethylammonium tosylate in 30% MeOH/THF electrolyte solution, and 2,6-lutidine as a proton scavenger. All of the reactions were complete after the passage of 2.0 F/mol of charge. Five- and six-membered-ring products **2a**−**d** were generated in good to excellent yields.[7] As in cases involving carbon−carbon bond formation, the generation of six-membered-ring products proved more difficult than formation of the analogous five-membered rings.

Scheme 1



Scheme 2



1a. R=Me; n=1	**2a.** 96% (5:1 mix of t/c isomers)
1b. R=CH$_2$Ph; n=1	**2b.** 95% (10:1 mix of t/c isomers)
1c. R=H; n=2	**2c.** 80% (NMR yield)
1d. R=CH$_2$Phe; n=2	**2d.** 51% (6:1 mix of t/c isomers)
1e. R=H; n=3	**2e.** --

For **1a**, **1b**, and **1d** the major product obtained had trans-stereochemistry. For the five-membered-ring cases, the trans-stereochemistry of the major product was established using a NOESY experiment. Since both isomers were readily available, the magnitude of the NOE between the two ring methine protons provided a nice handle for making the assignment. For the six-membered-ring product, the stereochemistry of the major product was established as trans using the coupling constants for the methine proton α to the ring oxygen (2.7 Hz for the interaction with the acetal methine and 9.3 Hz for the interaction with the ring methine β to the oxygen). At the present time, it is not clear whether the stereochemistry of the product is the result of a transition state with all of the groups equatorial[8] or the result of thermodynamic control.[9]

The cyclization reactions were not capable of making seven-membered-ring products. For example, the oxidation of substrate **1e** led to the formation of products derived from methanol trapping of the enol ether radical cation. This result suggested that the alcohol group was not as reactive a trapping group for the radical cation as either a second enol ether[10] or a furan ring.[11] Cyclization reactions using either of these trapping groups were capable of generating seven-membered-ring products. Overall, the reactivity of the alcohol for the radical cation intermediate appeared to be about the same as that of an allylsilane terminating group.[10] Allylsilanes also cleanly afford five- and six-membered rings but fail to make more challenging seven-membered rings. This observation was consistent with the solvent effects observered for the reactions. In the past, we have found that the most

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[1] For recent references see: (a) Frey, D. A.; Reddy, S. H. K.; Moeller, K. D. *J. Org. Chem.* **1999**, *64*, 2805. (b) Reddy, S. H. K.; Moeller, K. D. *Tetrahedron Lett.* **1998**, *39*, 8027. For a review see: (c) Moeller, K. D. *Top. Curr. Chem.* **1997**, *185*, 49.

[2] For a review see: (a) Elliot, M. C. *J. Chem. Soc., Perkin Trans. 1* **1998**, 4175. For recent methodology involving the synthesis of furans and pyrans: (b) Micalizio, G. C.; Roush, W. R. *Org. Lett.* **2000**, *2*, 461. (c) Cloninger, M. J.; Overman, L. E. *J. Am. Chem. Soc.* **1999**, *121*, 1092. (d) Nakada, M.; Iwata, Y.; Takano, M. *Tetrahedron Lett.* **1999**, *40*, 9077. (e) Trost, B. M.; Pinkerton, A. B. *J. Am. Chem. Soc.* **1999**, *121*, 10842. (f) Crich, D.; Huang, X.; Newcomb, M. *Org. Lett.* **1999**, *1*, 225.

[3] Hudson, C. M.; Moeller, K. D. *J. Am. Chem. Soc.* **1994**, *116*, 3347.

[4] The substrates were synthesized using a Wittig reaction on the corresponding lactol. Moeller, K. D.; Tinao, L. V. *J. Am. Chem. Soc.* **1992**, *114*, 1033.

[5] For a complementary approach to furans using a Wittig reaction followed by a Michael reaction see: (a) Georges, M.; Tam, T. F.; Fraiser-Reid, B. *J. Org. Chem.* **1985**, *50*, 5754. (b) Bloch, R.; Seck, M. *Tetrahedron* **1989**, *45*, 3731.

[6] A 100 PPI electrode was used (available from The Electrosynthesis Co., Inc.). The preparative electrolyses were conducted utilizing a Model 630 coulometer, a Model 410 potentiostatic controller, and a Model 420A power supply purchased from the Electrosynthesis Co., Inc.

[7] The yield of **2c** was determined by proton NMR using an internal standard due to the volatility of the product. All of the other yields reported represent the amount of pure product isolated from the reaction.

[8] For an example of an enol ether radical cation derived cyclization under kinetic control see ref 1a.

[9] For an example of an enol ether radical cation derived cyclization under thermodynamic control see ref 3.

[10] New, D. G.; Tesfai, Z.; Moeller, K. D. *J. Org. Chem.* **1996**, *61*, 1578.

[11] Hudson, C. M.; Marzabadi, M. R.; Moeller, K. D.; New, D. G. *J. Am. Chem. Soc.* **1991**, *113*, 7372.

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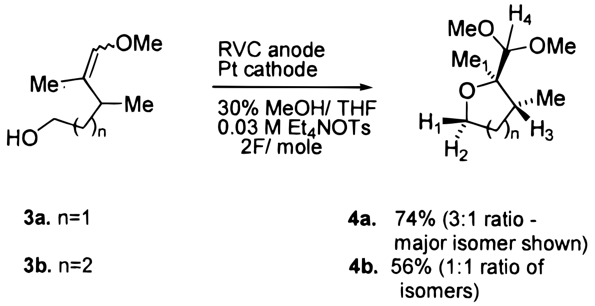
Scheme 3

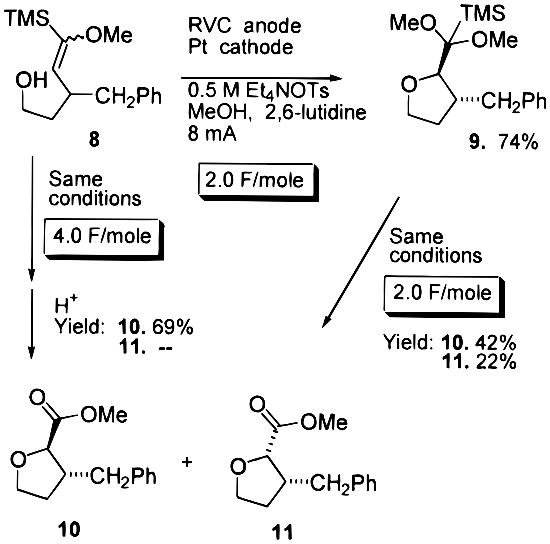


reactive terminating groups (enol ethers and furan rings) tolerate the use of pure methanol as the solvent. Less reactive terminating groups (allylsilanes, simple alkyl olefins, styrenes, etc.) require the use of a cosolvent to reduce the concentration of methanol around the electrode surface and hence slow the rate of solvent trapping of the radical cation. In the current cyclization reactions, it was found that the use of a cosolvent was essential. Even the five-membered-ring cyclization reactions did not proceed well in pure methanol solution.

A second method for determining the reactivity of a terminating group for the enol ether radical cation involves challenging the cyclization reaction to form a quaternary carbon (Scheme 3).[12] In the current case, the cyclization reaction to form a five-membered ring and a quaternary carbon (substrate **3a**) proceeded in a 74% isolated yield.[13] Interestingly, this reaction again led to a 3:1 ratio of stereoisomers with the trans-product predominating. As in the earlier experiments, the stereochemistry of the major product was established with the use of a NOESY experiment. This assignment was based on NOE cross-peaks between H_1 and H_3, H_3 and H_4, and H_2 and Me_1. Interestingly, when the cis- and trans-enol ether isomers of the substrate were separated and the electrolysis reaction repeated on each independently, the trans-enol ether and cis-enol ether substrates led to the same ratio of products. Either the enol ether stereochemistry was lost after the radical cation was formed, or the reaction was under thermodynamic control.

The reactions also proved to be compatible with the formation of both a quaternary carbon and a six-membered ring (substrate **3b**). In this case, a 56% isolated yield of the product was generated: a result that placed the reactivity of the alcohol for the radical cation intermediate between that of an enol ether trapping group which could also generate both a quaternary carbon and a six-membered ring and an allylsilane trapping group which could not.[12]

Scheme 4



The reactions could also be initiated by the oxidation of a ketene acetal equivalent. To this end, the oxidation of substrate **8** using the electrolysis conditions described above led to a 74% yield of product **9** (Scheme 4).[13] The reaction led mainly to the trans-product. An ca. 5% yield (by NMR) of a minor isomer, tentatively assigned as the cis-isomer, was obtained. Product **9** was reexposed to the electrolysis conditions to generate products **10** and **11** in a 64% isolated yield. Interestingly, this reaction scrambled the stereochemistry at C_2 of the tetrahydrofuran ring.[14]

The methyl ester products could be formed directly by oxidizing **8** using 4.0 F/mol of charge. In this case, an acidic workup of the electrolysis (aqueous. HCl) converted the cis-methyl ester product **11** into product **10** prior to isolation. By using these conditions, a 69% yield of **10** was obtained.

Finally, the cyclization reactions were compatible with the use of a 6-V lantern battery as the power supply.[15] All other conditions were identical with those outlined above.[13] With the battery, the oxidation of substrates **1a** and **2a** afforded a 74% and a 55% (with 25% recovered starting material) yield of the cyclized products, respectively. The success of these reactions indicated that the effectiveness of a cyclization could be determined without the need for specialized equipment.

In conclusion, the anodic oxidation of an enol ether can be used to trigger the formation of both tetrahydrofuran and tetrahydropyran heterocycles. Because the cyclization reactions allow for the formation of a bond between a nucleophilic oxygen and the normally nucleophilic carbon α to a carbonyl, the methodology nicely compliments existing chemical routes to related ring systems. Efforts to utilize this methodology for the synthesis of natural products and to extend the work to the formation of other heterocyclic molecules are underway.

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Supporting Information Available: A sample experimental electrochemical procedure along with spectral data for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Tinao-Wooldridge, L. V.; Moeller, K. D.; Hudson, C. M. *J. Org. Chem.* **1994**, *59*, 2381.

(13) These reactions did not require the use of 2,6-lutidine as a proton scavanger.

(14) For a mechanism see: Yoshida, J. *Top. Curr. Chem.* **1994**, *170*, 39.

(15) Frey, D. A.; Wu, N.; Moeller, K. D. *Tetrahedron Lett.* **1996**, *37*, 8317.