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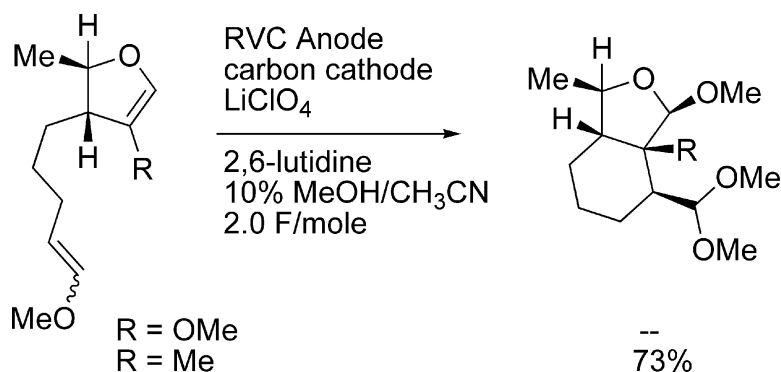
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Intramolecular Anodic Olefin Coupling Reactions: The Effect of Polarization on Carbon–Carbon Bond Formation

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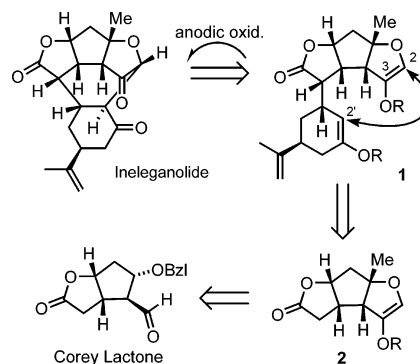Received August 15, 2007; E-mail: moeller@wustl.edu

The intramolecular anodic olefin coupling reaction is an intriguing method for making new carbon–carbon bonds and generating new ring skeletons.[1,2] The reactions have been initiated by the oxidation of either an enol ether or a ketene acetal, and the ensuing radical cation intermediates were trapped with a variety of nucleophiles. The cyclizations are compatible with the synthesis of fused and bridged bicyclic compounds, the generation of quaternary carbons,[3] and the use of very simple reaction setups.[4]

In principle, intramolecular anodic olefin coupling reactions can serve as a versatile tool for synthesis of a wide variety of complex molecular architectures. For example, consider the retrosynthesis of ineleganolide[5] shown in Scheme 1. In this plan, an intramolecular anodic olefin coupling reaction would be used to generate a new bond between C_2 and $C_{2'}$ in **1**. While both C_2 and C_3 of the five-membered ring ene diol ether can potentially participate in bond formation, molecular modeling suggests that the strain of the ring system would favor seven-membered ring formation. However, an enediol ether moiety like the one present in the five-membered ring of **1** has never before been employed in an oxidative cyclization reaction. Does the use of this new initiating group and new radical cation intermediate interfere with the ability of the reaction to make carbon–carbon bonds? Any effort to explore the synthetic potential of an oxidative cyclization like the one proposed in Scheme 1 must begin by addressing this question.
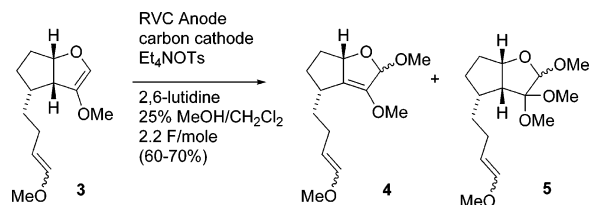
Previous studies comparing cyclizations originating from enol ether derived radical cations to cyclizations originating from ketene acetal derived radical cations indicated that adding a second donating group to the initiating olefin and subsequent radical cation aided carbon–carbon bond formation.[2a] But in those cases, the extra electron-donating group on the double bond not only increased the electron density of the double bond and subsequent radical cation but also increased the polarization of the system. Is this important? The cyclization proposed in Scheme 1 provided us with an opportunity to investigate this question. We report herein that polarization of the radical cation is the determining factor in governing carbon–carbon bond formation in an intramolecular anodic olefin coupling reaction and that enediol ether type substrates can serve as participants in the cyclization if properly substituted.

Believing that the success of N,O-ketene acetal derived cyclizations stemmed from the electron-richness of the intermediate radical cation, our first attempt at the cyclization sought to answer questions about the use of an enediol ether initiating group while demonstrating the utility of conformational constraints for controlling the regiochemistry of the reaction. Namely, bicyclic substrate **3** was synthesized and submitted to the anodic oxidation reaction (Scheme 2). Surprisingly, the oxidation of **3** generated no cyclized product. Instead, a 60–70% yield of uncyclized material was generated as an inseparable mixture. While inseparable, the products could be tentatively assigned as elimination and solvent-trapping products **4** and **5**.[6] While rigorous characterization was not possible, all of the products observed still possessed the side chain enol ether moiety. The radical cation intermediate was "well-behaved" in that
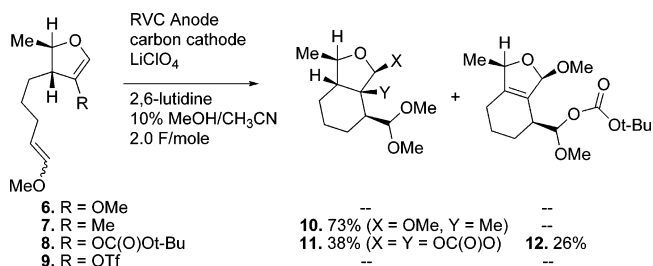
Scheme 1

Scheme 2

Scheme 3

6. R = OMe	--	--
7. R = Me	**10.** 73% (X = OMe, Y = Me)	--
8. R = OC(O)Ot-Bu	**11.** 38% (X = Y = OC(O)O)	**12.** 26%
9. R = OTf	--	--

it led cleanly to monomeric products. There was no evidence of radical cation polymerization. So what stopped the cyclization? Was the conformational constraint too rigid in that it prevented approach of the enol ether trapping group to the radical cation, or did the second electron-donating group on the radical cation intermediate hinder carbon–carbon bond formation?

In order to address this question, substrates **6–9** were studied (Scheme 3).[7] Once again, the substrate having an additional methoxy substituent on the five-membered ring double bond (**6**) led to none of the desired cyclized product. Instead, a 60–70% yield of uncyclized materials again arising from elimination and solvent trapping of the radical cation resulted. For comparison, anodic oxidation of substrate **7** cleanly led to the cyclized product in a 73% isolated yield, a result that was consistent with earlier reactions leading to fused- and bridged-bicyclic ring skeletons.[8] Clearly, there was no conformational bias in this system preventing the cyclization. So in direct contrast to earlier results using ketene acetal substrates, the presence of a second donor group on the radical cation derived from substrate **6** stopped carbon–carbon bond
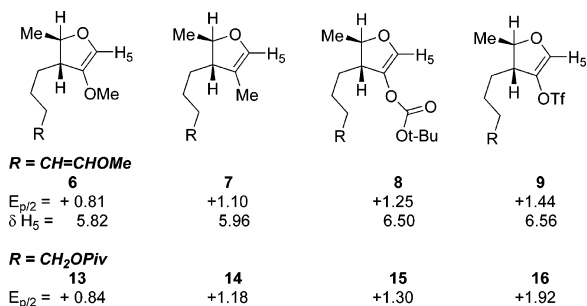
R = CH=CHOMe			
6	**7**	**8**	**9**
$E_{p/2}$ = + 0.81	+1.10	+1.25	+1.44
δ H5 = 5.82	5.96	6.50	6.56
R = CH2OPiv			
13	**14**	**15**	**16**
$E_{p/2}$ = + 0.84	+1.18	+1.30	+1.92

Figure 1.

formation. This observation suggested that it was polarization of the radical cation in the ketene acetal derived cyclizations that favored carbon−carbon bond formation. This was a testable idea.

In substrate **8**, the methoxy group used in substrate **6** was replaced with a *t*-butoxycarbonyl substituent. Ester substituents are known to be electronically neutral. For example, the placement of a pivaloyloxy substituent on an electron-rich aromatic ring leads to no change in the oxidation potential of the aromatic ring.[9] Hence, in the current substrates the use of such a group should lead to a less-electron-rich but more polar initiating olefin (and subsequent radical cation). This effect is illustrated in Figure 1. The $E_{p/2}$ data (measured by cyclic voltammetry vs Ag/AgCl)[10] provides an indication of the electron-richness of the substrate, while the chemical shift of the proton at C2 provides evidence for the polarity of the double bond (the greater the positive charge character at C2, the greater the chemical shift). This data shows that in moving from substrate **6** to substrate **9**, the five-membered ring enol ether becomes significantly less electron-rich and significantly more polar. Hence, if polarization determines the degree of carbon−carbon bond formation and not the electron-richness of the double bond, then the oxidation of substrate **8** should lead to carbon−carbon bond formation despite what happened during the oxidation of substrate **6**. This was indeed the case (Scheme 3), and the anodic cyclization led to a 62% yield of cyclized product as a mixture of a cyclic carbonate (**11**) and elimination product (**12**). The yield was unoptimized due to the instability of the products. A proton NMR of the crude reaction mixture showed no remaining side chain enol ether or starting enediol ether double bond protons. Clearly, no uncyclized products from either an elimination reaction or solvent trapping of the radical cation were generated.

As in the case of the ketene acetal substrates studied earlier,[2a] cyclic voltammetry data indicated that the greater cyclization efficiency of the reactions originating from **7** and **8** was due more to an increase in the stability of the intermediate radical cations in methanol than to an increase in the rate of the cyclization reactions. This conclusion was reached by observing the shift in potential for the five-membered ring double bond caused by the addition of the side-chain trapping group. For a reaction involving an electron transfer followed by a fast chemical reaction, the potential measured for the substrate depends on the rate of the chemical reaction. Faster chemical reactions lead to larger shifts in potential.[10] Hence, the shift in potential measured for substrates **6**−**8** relative to those measured for substrates **13**−**15** lacking the side-chain enol ether provides a measure of the relative rates of the cyclizations. With this in mind, the potential measured for substrate **6** was 30 mV lower than that for **13**, a shift attributed to a cyclization reaction since the CV experiment was run in the absence of methanol. The shift for substrate **7** relative to **14** was 80 mV and for substrate **8** relative to **15** only 50 mV. The differences in magnitude for these shifts are small indicating that all three cyclizations occur with comparable rates. Thus, the complete lack of cyclized product from

the preparative oxidation of **6** must be the result of a faster methanol trapping reaction relative to the oxidations of **7** and **8**. This observation indicates that a preparative cyclization originating from **6** might be successful if the methanol solvent can be avoided.

Finally, there were limits to how far the idea of polarization vs electron-richness of the enediol ether moiety could be pushed. In the case of substrate **9**, the triflate group proved to be electron-withdrawing and raised the oxidation potential of the enediol ether to a point where it was significantly higher than the potential of the enol ether "trapping group". For example, compare the pivolyl substituted substrate **16** with compound **9**. The $E_{p/2}$ value for **16** of +1.92 V vs Ag/AgCl is the oxidation potential of the triflate substituted five-membered ring double bond. The $E_{p/2}$ value for **9** of +1.44 V vs Ag/AgCl is consistent with oxidation of the methoxy enol ether on the side chain.[11] In the case of **9**, preparative oxidation led to methoxylation of the side chain enol ether and no oxidation of the five-membered ring double bond. The lack of cyclization originating from a side-chain radical cation is consistent with earlier anodic olefin coupling reactions that behaved like radical cyclizations in that they were very sensitive to steric hindrance on the terminating olefin.[12]

In conclusion, we have found that anodic olefin coupling reactions do tolerate a second donor group on the olefin leading to the radical cation, but only if such a group increases or maintains the polarization of the radical cation. Hence, for a ketene acetal type substrate, it is beneficial to add the second donor group, but for an enediol type substrate like the one proposed for the synthesis of ineleganolide, it is important to make sure that the second oxygen substituent on the initiating olefin is electronically neutral. With this information, we are now in position to address the regiochemistry of the cyclization proposed in Scheme 1. This work is currently underway.

Supporting Information Available: The procedures for synthesizing substrates **6**−**9**, a general procedure for the electrolysis reaction, and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For a review, see: (a) Moeller, K. D. *Tetrahedron* **2000**, *56*, 9527. For a recent review of electroorganic synthesis, see: (b) Sperry, J. B; Wright, D. L. *Chem. Soc. Rev.* **2006**, *35*, 605.

(2) For recent work, see: (a) Huang, Y.; Moeller, K. D. *Tetrahedron* **2006**, *62*, 6536. (b) Brandt, J. D.; Moeller, K. D. *Org. Lett.* **2005**, *7*, 3553 and references therein.

(3) For examples, see: (a) Mihelcic, J.; Moeller, K. D. *J. Am. Chem. Soc.* **2004**, *126*, 9106. (b) Wright, D. L.; Whitehead, C. R.; Sessions, E. H.; Ghiviriga, I.; Frey, D. A. *Org. Lett.* **1999**, *1*, 1535. (c) Hughes, C. C.; Miller, A. K.; Trauner, D. *Org. Lett.* **2005**, *7*, 3425. (d) Miller, A. K.; Hughes, C. C.; Kennedy-Smith, J. J.; Gradl, S. N.; Trauner, D. *J. Am. Chem. Soc.* **2006**, *128*, 17057.

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

(5) Duh, C.-Y.; Wang, S.-K.; Chia, M.-C.; Chiang, M. Y. *Tetrahedron Lett.* **1999**, *40*, 6033.

(6) Solvent trapping and elimination are the typical products generated from failed cyclizations. For examples, see: (a) New, D. G.; Tesfai, Z.; Moeller, K. D. *J. Org. Chem.* **1996**, *61*, 1578−1598. (b) Reddy, S. H. K.; Chiba, K.; Sun, Y.; Moeller, K. D. *Tetrahedron* **2001**, *57*, 5183.

(7) For synthetic details, please see the Supporting Information.

(8) See reference 6b, as well as the following: (a) Frey, D. A.; Reddy, S. H. K.; Wu, N.; Moeller, K. D. *J. Org. Chem.* **1999**, *64*, 2805. (b) Tinao-Wooldridge, L. V.; Moeller, K. D.; Hudson, C. M. *J. Org. Chem.* **1994**, *59*, 2381−2389.

(9) Moeller, K. D.; Wang, P. W.; Tarazi, S.; Marzabadi, M. R.; Wong, P. L. *J. Org. Chem.* **1991**, *56*, 1058−1067.

(10) All CV data was measured using a BAS 100B/W electrochemical analyzer, Pt working and auxiliary electrodes, a Ag/AgCl reference electrode, a 0.1 M LiClO4 in acetonitrile electrolyte solution, a substrate concentration of 0.025 M, and a sweep rate of 25 mV/s.

(11) For examples, see refs 2a, 6b, and Moeller, K. D.; Tinao, L. V. *J. Am. Chem. Soc.* **1992**, *114*, 1033.

(12) Sun, Y.; Moeller, K. D. *Tetrahedron Lett.* **2002**, *43*, 7159.

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