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Intramolecular Anodic Olefin Coupling Reactions: The Use of a Nitrogen Trapping Group

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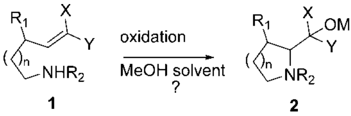
Anodic oxidation reactions can be used to generate reactive radical cation intermediates and trigger interesting new umpolung reactions.[1] For example, we have found that the oxidation of electron-rich enol ethers and ketene acetals can lead to a variety of cyclization reactions involving the formation of either carbon−carbon[2] or carbon−oxygen bonds.[3] In each case, the oxidation reaction resulted in the coupling of two groups normally thought to be nucleophiles. With this in mind, we hoped to build cyclic amino acid derivatives by oxidatively coupling an enol ether or ketene acetal derivative to a nitrogen-based nucleophile (Scheme 1). Initial attempts to accomplish such a transformation failed.

When an oxidation of an amine or methoxy amine was performed in hopes of adding a nitrogen-based radical or radical cation to an enol ether,[4−6] decomposition of the enol ether dominated the reaction. When the nitrogen was substituted with an electron-withdrawing group and the oxidation channeled toward the enol ether, decomposition of the enol ether derived radical cation prior to nitrogen trapping dominated the reaction. In both cases, a poor yield of cyclized product was obtained. We report here that these problems can be solved with the use of more basic electrolysis conditions and that anodic cyclization reactions can be used to build proline derivatives by generating new carbon−nitrogen bonds.

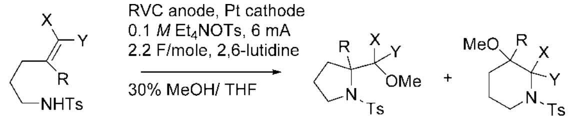
Initial efforts to improve the cyclization reactions varied the substituents on the double bond in **1**. We have found that the nature of the substituents on a radical cation can dramatically alter its reactivity.[2b,c,e,g] The study was started by examining substrates **3a**−**d** (Scheme 2). An enol ether, a vinylsulfide, and a ketene dithioacetal were chosen as the olefin coupling partners for the reaction. A tosylated amine was used as the nucleophile because of its known effectiveness for trapping electrophiles.[7] As in earlier studies, the oxidation of the enol ether substrate **3a** using a reticulated vitreous carbon anode, a platinum cathode, tetraethylammonium tosylate as electrolyte, 2,6-lutidine as an proton scavenger, and 30% methanol/THF solvent led to a mixture of products out of which only a 20% isolated yield of the desired cyclization product **4a** was obtained. The reaction was conducted at a constant current of 6 mA until 2.2 F/mol of current had been passed. The yield of the reaction could be improved to 26% by using methanol as the reaction solvent; however, a much more significant improvement in the yield of the cyclization was obtained when thioenol ether substrate **3b** was oxidized. Using the same conditions as those for the initial oxidation of **3a**, a 54% isolated yield of product **4b** was obtained. This result was consistent with earlier observations that more polarized radical cation intermediates tend to favor carbon−carbon bond formation while less polarized radical cations tend to favor carbon−heteroatom bond formation.[2b]

To complete the initial study, the anodic oxidation of dithioketene acetal substrate **3c** was examined. In this case, only a 14% yield of the desired product was obtained. In addition, 4% of a dimethoxylated product (**4** where R = OMe) was formed.[8] This product resulted from the elimination of methanol from **4c** followed by a second oxidation. To avoid the elimination of methanol from **4c**, substrate **3d** was synthesized and oxidized. The reaction led to a 43% yield of an ∼1/1.3 mixture of cyclized products **4d** and **5d**.

Scheme 1

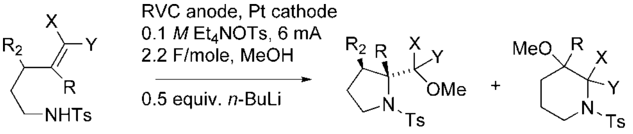


Scheme 2



3a. X = H, Y = OMe, R = H	**4a**. 20%	**5a**. --
3b. X = H, Y = SMe, R = H	**4b**. 54%	**5b**. --
3c. X = Y = -S$(CH_2)_3$S-, R = H	**4c**. 14%	**5c**. --
3d. X = Y = -S$(CH_2)_3$S-, R = Me	**4d**. 19%	**5d**. 24%

Scheme 3



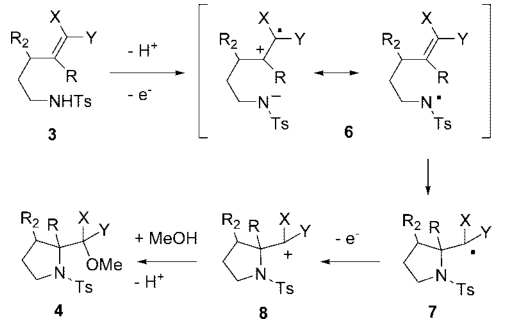
3a. X = H, Y = OMe, R = H, R_2 = H	**4a**. 82%	**5a**. --
3b. X = H, Y = SMe, R = H, R_2 = H	**4b**. 90%	**5b**. --
3c. X = Y = -S$(CH_2)_3$S-, R = H, R_2 = H	**4c**. 50%[9]	**5c**. --
3d. X = Y = -S$(CH_2)_3$S-, R = Me, R_2 = H	**4d**. 73%	**5d**. 7%
3e. X = H, Y = OMe, R = Me, R_2 = H	**4e**. 77%	**5e**. --
3f. X = H, Y = SMe, R = Me, R_2 = H	**4f**. 89%	**5f**. --
3g X = Y = -S$(CH_2)_3$S-, R = R_2 = Me	**4g**. 83%	**5g**. --

Six-membered ring product **5d** resulted from methanol trapping of the radical cation competing with trapping by the tosylamine. This observation suggested that the reactions might benefit from conditions that increased the nucleophilicity of the nitrogen trapping group. With this in mind, the reaction conditions were made more basic by replacing the 2,6-lutidine acid scavenger with LiOMe. The LiOMe was generated *in situ* by adding 0.5 equiv of *n*-BuLi to the reaction mixture. LiOMe was selected as the base because it would not be consumed in the reaction. During the electrolysis, methanol is reduced at the cathode. Hence, for every proton scavenged at the anode a new methoxide ion would be generated at the cathode.

The change had a dramatic impact on the yield of the cyclization reactions (Scheme 3). For example, the oxidation of **3a** led to an 82% isolated yield of the desired cyclized product **4a**. Anodic oxidation of **3b** led to a 90% yield of **4b**. Once again, the oxidation of **3c** was plagued by the elimination of methanol from the initially formed product (**4c**, R = H). When the conditions for the experiment shown in Scheme 3 were used, a 22% yield of cyclized product (**4c**, R = H) was obtained along with 8% of the

10.1021/ja806259z CCC: $40.75

Scheme 4



dimethoxylated product (**4** where R = OMe, R_2 = H). The total yield of cyclized product isolated could be improved by reducing the concentration of electrolyte in the reaction to 0.03 M Et_4NOTs in methanol. With these conditions, a 50% yield of **4c** was obtained along with 16% of the dimethoxylated product. Clearly, the initial cyclization proceeded well. Removing the possibility for the elimination again led to a significant improvement in the reaction. Anodic oxidation of **3d** led to a 73% isolated yield of the five-membered ring product **4d** along with 7% of **5d**.

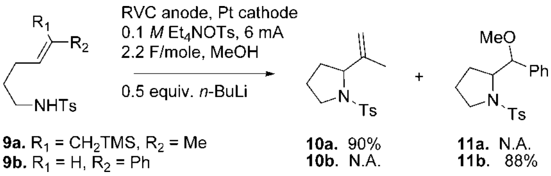
The use of the enol ether and thioenol ether initiating groups also proved compatible with the formation of a tetrasubstituted carbon. The anodic oxidation of both substrates **3e** and **3f** led to the desired five-membered ring product in high yield. As in the oxidation of **3a** and **3b**, the best yield was obtained using the less polar thioenol ether substrate.

In line with our rationale for using the more basic reaction conditions, the use of LiOMe in the reactions is thought to improve the reactions by deprotonating the sulfonamide thereby increasing the rate of the cyclization (Scheme 4). The cyclization can be thought of as occurring by the formation of a olefin radical cation that is then trapped by the nitrogen anion or by the formation of a nitrogen-based radical that then adds to the electron-rich olefin. These two alternatives are resonance forms of each other. The cyclization generates a radical (**7**) which is then oxidized to form **8** and then trapped by solvent to afford the final product.

The oxidation of substrate **3g** suggests that an increase in the trapping of **8** might also play a role in improving the yield of reactions using LiOMe. The oxidation of **3g** in methanol solvent led to **4g** in an 83% isolated yield (Scheme 3). When the solvent for this transformation was changed to 30% methanol in THF, a change made to slow down methanol trapping of the intermediates generated, only a 28% yield of **4g** was obtained. Slowing solvent trapping before the cyclization reaction should not hurt the yield of cyclic product obtained. However, slowing solvent trapping of **8** could allow more time for its decomposition thereby decreasing the yield of **4g**. Hence, the oxidations of **3g** were most consistent with a cyclization that proceeded quickly (faster than methanol trapping of the radical cation in methanol solvent) but then required rapid trapping of the cationic intermediate generated after the cyclization.

Product **4g** was obtained as a single isomer with the stereochemistry illustrated in Scheme 3. This stereochemistry was consistent with earlier cyclizations employing alcohol nucleophiles and ketene dithioacetals.[3] Since substrates like **3** can be made nicely in an asymmetric fashion,[3a] the oxidation of **3g** highlights the opportunity the cyclizations afford for building chiral amino acid derivatives.

Scheme 5



Finally, the oxidation of substrates **9a** and **9b** (Scheme 5) demonstrated that the oxidative coupling reactions are compatible with other electron-rich olefins. In the case of **9a**, the anodic oxidation of an allylsilane led to the cyclization reaction. In **9b**, oxidation of a styrene moiety triggered the cyclization.

In conclusion, we have found that anodic olefin coupling reactions can take advantage of nitrogen trapping groups and lead to the formation of proline derivatives. The reactions benefit from the use of a less polar radical cation intermediate and the use of more basic reaction conditions. Efforts to extend this work to the synthesis of six-membered rings and the construction of more complex natural products and peptidomimetics are underway.

Supporting Information Available: The procedures for synthesizing substrates **3a**−**3g** and **9a,b**, a general procedure for the electrolysis reaction, and spectral data for all new compounds are included. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For a recent reviews of the use of electrochemistry in synthesis, see: (a) Sperry, J. B.; Wright, D. L. *Chem. Soc. Rev.* **2006**, *35*, 605. (b) Yoshida, J.; Kataoka, K.; Horcajada, R.; Nagaki, A. *Chem. Rev.* **2008**, *108*, 2265.

(2) For a review of early work, see: (a) Moeller, K. D. *Tetrahedron* **2000**, *56*, 9527. For selected recent efforts, see: (b) Tang, F.; Moeller, K. D. *J. Am. Chem. Soc.* **2007**, *129*, 12414. (c) Wu, H.; Moeller, K. D. *Org. Lett.* **2007**, *9*, 4599. (d) Tang, F.; Chen, C.; Moeller, K. D. *Synthesis* **2007**, 3411. (e) Huang, Y.; Moeller, K. D. *Tetrahedron* **2006**, *62*, 6536. (f) Mihelcic, J.; Moeller, K. D. *J. Am. Chem. Soc.* **2004**, *126*, 9106–9111. (g) Huang, Y.; Moeller, K. D. *Org. Lett.* **2004**, *6*, 4199.

(3) (a) Xu, H.-C.; Brandt, J. D.; Moeller, K. D. *Tetrahedron Lett.* **2008**, *49*, 3868. (b) Brandt, J. D.; Moeller, K. D. *Heterocycles* **2006**, *67*, 621. (c) Brandt, J. D.; Moeller, K. D. *Org. Lett.* **2005**, *7*, 3553. (d) Liu, B.; Duan, S.; Sutterer, A. C.; Moeller, K. D. *J. Am. Chem. Soc.* **2002**, *124*, 10101. (e) Duan, S.; Moeller, K. D. *J. Am. Chem. Soc.* **2002**, *124*, 9368. (f) Duan, S.; Moeller, K. D. *Org. Lett.* **2001**, *3*, 2685. (g) Sutterer, A.; Moeller, K. D. *J. Am. Chem. Soc.* **2000**, *122*, 5636.

(4) For anodic cyclizations between methoxy amines and styrene derivatives, see: (a) Tokuda, M.; Miyamoto, T.; Fujita, H.; Suginome, H. *Tetrahedron* **1991**, *47*, 747. (b) Tokuda, M.; Fujita, H.; Miyamoto, T.; Suginome, H. *Tetrahedron* **1993**, *49*, 2413.

(5) For related (nonoxidative) cyclizations involving aminium radical cations, see: (a) Ha, C.; Musa, O. M.; Martinez, F. N.; Newcomb, M. *J. Org. Chem.* **1997**, *62*, 2704. (b) Newcomb, M.; Tanaka, N.; Bouvier, A.; Tronche, C.; Horner, H. H.; Musa, O. M.; Martinez, F. N. *J. Am. Chem. Soc.* **1996**, *118*, 8505. (c) Horner, J. M.; Martinez, F. N.; Musa, O. M.; Newcomb, M.; Shahin, H. E. *J. Am. Chem. Soc.* **1995**, *117*, 11124. (d) Newcomb, M.; Marquartd, D. J.; Deeb, T. M. *Tetrahedron* **1990**, *46*, 2329. (e) Newcomb, M.; Marquartd, D. J.; Deeb, T. M. *Tetrahedron* **1990**, *46*, 2927. (f) Newcomb, M.; Deeb, T. M. *J. Am. Chem. Soc.* **1987**, *109*, 3163.

(6) For a detailed comparison between aminium radical cation derived cyclizations and amidyl radical derived cyclizations, see: Horner, J. H.; Musa, O. M.; Bouvier, A.; Newcomb, M. *J. Am. Chem. Soc.* **1998**, *120*, 7738.

(7) (a) Liu, G.; Stahl, S. S. *J. Am. Chem. Soc.* **2007**, *129*, 8328. (b) Fix, S. R.; Brice, J. L.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 164.

(8) For spectral data, see the Supporting Information.

(9) Optimization of the yield in this case required the use of 0.03 M Et_4NOTs. All other conditions were the same.

JA806259Z