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Anodic Cyclization Reactions: Reversing the Polarity of Ketene Dithioacetal Groups

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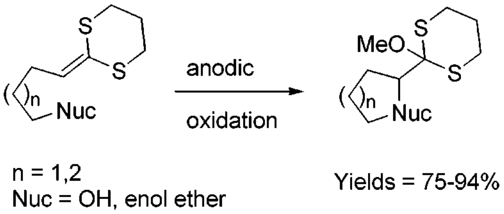
ABSTRACT



Intramolecular coupling reactions of ketene dithioacetal groups with enol ether and alcohol nucleophiles have been studied. The reactions were initiated by an anodic oxidation of the ketene dithioacetal and proved to be compatible with the formation of five- or six-member rings, as well as the stereoselective generation of quaternary carbons.

While the anodic oxidation of alkyl and silyl enol ethers has been used to make a variety of new ring systems,[1,2] similar reactions utilizing ketene acetal functional groups are rare.[3−5] This is disappointing since initiating an oxidative cyclization reaction by oxidizing a ketene acetal derivative has the potential to provide a direct route to new rings having carboxylic acid derivatives as substituents as well as provide useful solutions to a number of the synthetic problems encountered with enol ether based cyclization reactions. For example, we recently demonstrated that the use of a ketene dithioacetal initiating group provided an effective solution for the key problem encountered when trying to employ the anodic coupling of two enol ether moieties to construct the key bicyclo[3.2.1]octane portion of scopadulcic acid B (Figure 1).[3b,6] While the initial cyclization reactions proceeded well (Scheme 1, eq 1), the products generated could not be used to further elaborate the natural product. The use of both an enol ether oxidation for initiating the cyclization reaction and an enol ether for trapping the radical cation generated led to a product having a pair of dimethoxy acetal

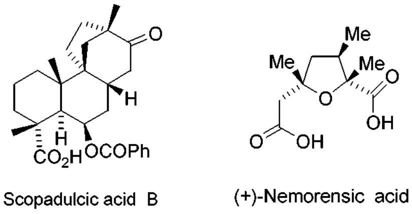


Figure 1. Potential natural product targets.

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(1) For a review of synthetic applications of anodic electrochemistry, see: Moeller, K. D. *Tetrahedron* **2000**, *56*, 9527.

(2) For selected examples, see: (a) Hudson, C. M.; Marzabadi, M. R.; Moeller, K. D.; New, D. G. *J. Am. Chem. Soc.* **1991**, *113*, 7372. (b) Frey, D. A.; Reddy, S. H. K.; Moeller, K. D. *J. Org. Chem.* **1999**, *64*, 2805. (c) Moeller, K. D.; Tinao, L. V. *J. Am. Chem. Soc.* **1992**, *114*, 1033. (d) New, D. G.; Tesfai, Z.; Moeller, K. D. *J. Org. Chem.* **1996**, *61*, 1578.

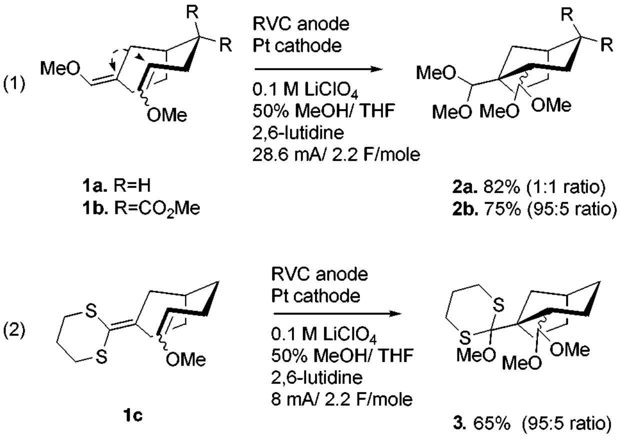
(3) Silyl-substituted enol ethers have been used in anodic coupling reactions. For a single example using an oxygen nucleophile, see: (a) Sutterer, A.; Moeller, K. D. *J. Am. Chem. Soc.* **2000**, *122*, 5636. For three examples leading to carbon−carbon bond formation, see: (b) Reddy, S. H. K.; Chiba, K.; Sun, Y.; Moeller, K. D. *Tetrahedron.* In press.

(4) A pair of cyclization reactions resulting from the intramolecular coupling of a ketene dithioacetal group with a trisubstituted olefin using ceric ammonium nitrate and a related coupling using a styrene terminating group have been reported: Snider, B. B.; Shi, B.; Quickley, C. A. *Tetrahedron* **2000**, *56*, 10127.

(5) For a single example of a cyclic ketene acetal being coupled to an allylsilane terminating group with the use of a vanadium(V) ester, see: Ryter, K.; Livinghouse, T. *J. Am. Chem. Soc.* **1998**, *120*, 2658.

10.1021/ol015925d CCC: $20.00

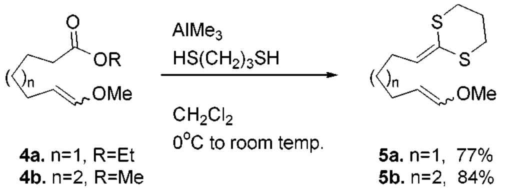
Scheme 1



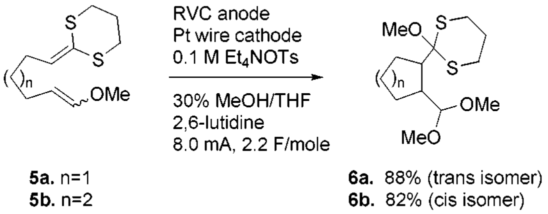
groups. All efforts to synthetically differentiate these groups met with failure. However, the use of a ketene dithioacetal as the initiating group for the cyclization reaction (Scheme 1, eq 2) completely circumvented this problem.[7] In this example, the anodic oxidation reaction led to the formation of a radical cation from the ketene dithioacetal that in turn was trapped by the side chain enol ether. Following trapping by methanol, loss of a second electron, and a second trapping with methanol step, the reaction afforded a cyclized product with one ortho ester group and one acetal. The ends of the cyclization were automatically differentiated. Interestingly, the reaction was also stereoselective even in the absence of the directing R-groups that were required for obtaining selectivity in the case of the bis-enol ether cyclizations (**1b**). This observation immediately led to questions concerning the generality of the process. Would other anodic cyclization reactions also show a greater degree of stereoselectivity when a ketene dithioacetal initiating group was employed as the initiating olefin, and what other trapping groups would be compatible with the oxidative cyclization reactions?

As a starting point for addressing these questions, substrates **5a** and **5b** were synthesized as outlined in Scheme 2.[8] Once in hand, the substrates (1 mmol) were oxidized at a reticulated vitreous carbon anode using an undivided cell (a three-neck round-bottom flask), a constant current of 8 mA, 0.1 M Et_4NOTs in a 30% methanol in tetrahydrofuran electrolyte solution, and 2,6-lutidine as a proton scavenger (Scheme 3).[9] By TLC both of the cyclization reactions illustrated were complete after 2.2 F/mol of electricity had been passed. Both cyclizations led to an excellent yield of the cyclized product and the generation of a single stereochemical isomer.

Scheme 2



Scheme 3



The stereochemistry of product **6a** was assigned as trans on the basis of a NOESY experiment. In this experiment, the acetal methine proton showed equal NOE interactions with both methine protons H_1 and H_2 (**6a**/ Figure 2). A similar set of interactions was not possible for the cis isomer. Typically, for the cis isomer the interaction between H_2 and the acetal methine cannot be observed.

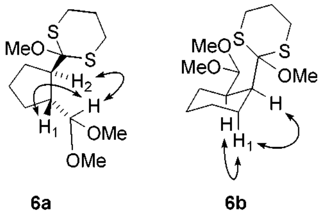


Figure 2. Key NOE interactions in compounds **6a** and **6b**.

In contrast to the five-membered ring case, NOESY data for **6b** indicated that the six-membered ring isomer formed had cis stereochemistry. As illustrated in Figure 2 (**6b**), NOE interactions between both of the methine protons and H_1 indicated that all three protons were on the same face of the molecule. Hence, the two substituents had to be cis to each other. While for clarity a single conformation is illustrated in Figure 2, the NOESY data obtained were consistent with two rapidly equilibrating conformations. At this time, it is not clear why the two cyclizations afford different selectivities, although steric issues would seem to significantly hinder

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(6) For previous syntheses of scopadulcic acid B, see: (a) Ziegler, F. E.; Wallace, O. B. *J. Org. Chem.* **1995**, *60*, 3626. (b) Overman, L. E.; Ricca, D. J.; Tran, V. D. *J. Am. Chem. Soc.* **1993**, *115*, 2042. For other related synthetic efforts, see: (c) Robichaud, A. J.; Meyers, A. I. *J. Org. Chem.* **1991**, *56*, 2607. (d) Abelman, M. M.; Overman, L. E. *J. Am. Chem. Soc.* **1988**, *110*, 2328. (e) Kucera, D. J.; O'Connor, S. J.; Overman, L. E. *J. Org. Chem.* **1993**, *58*, 5304.

(7) For a review on the use of ketene dithioacetals in synthesis, see: Kolb, M. *Synthesis* **1990**, 171.

(8) (a) For the conversion of esters to ketene dithioacetals, see: Corey, E. J.; Kozikowski, A. P. *Tetrahedron Lett.* **1975**, *16*, 925. (b) Substrates **4a** and **4b** were made from the commercially available alcohol esters.

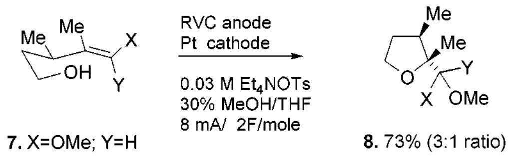
(9) (a) The oxidations were conducted using a Model 630 coulometer, a Model 410 potentiostatic controller, and a Model 420A power supply purchased from The Electrosynthesis Co., Inc. (b) For a simple setup to try electrochemical reactions using a battery as a power supply, see: Frey, D. A.; Wu, N.; Moeller, K. D. *Tetrahedron Lett.* **1996**, *37*, 8317.

the formation of a cis-isomer in the five-membered ring case. From both reactions, it was clear that the presence of the ketene dithioacetal initiating group dramatically influenced the stereochemical course of the reactions. Earlier enol ether−enol ether coupling reactions led to 1:1 mixtures of stereoisomers for the formation of both five- and six-membered rings.[2c,10]

Interestingly, the cyclization reactions illustrated in Scheme 3 required the use of THF as a cosolvent. Reactions performed in pure methanol solvent led to significantly decreased yields. This result suggested that the cyclization reactions were not as efficient as the previously studied enol ether−enol ether coupling reactions that did not require the use of a cosolvent. In addition to the choice of solvent, both the dryness of the electrolyte and the conditions used to workup the reactions influenced the yield of products **6a** and **6b**. Prior to the reactions, the electrolyte was dried in an oven for 12 h. For the workup, the crude reaction was concentrated and ether added to precipitate the electrolyte. The material was then filtered and immediately chromatographed using a silica gel column packed with 1% triethylamine in the solvent. In the case of **6a**, when these precautions were not taken the product was obtained as a mixture along with a cyclized ketene dithioacetal product formed by the elimination of methanol.

Having established that the use of a ketene dithioacetal initiating group influenced the stereochemistry of anodic carbon−carbon bond formation, we turned our attention to reactions that trapped the initial radical cation with an oxygen nucleophile.[3a] It was hoped that the use of a ketene dithioacetal initiating group would also improve the stereoselectivity of these reactions. For example, consider the cyclization reaction illustrated in Scheme 4. In this reaction, a 3:1 ratio of two tetrahydrofuran products was formed that favored a major product with the vicinal methyl groups cis to each other. While this stereochemistry matched what would be needed for applying the reaction to a synthesis of (+)-nemorensic acid (Figure 1),[11] the 3:1 ratio reflected a degree of selectivity that was too low for an efficient approach. It was suggested that the use of a ketene dithioacetal as the initiating group might improve this selectivity by making the olefin sterically larger and destabilizing the transition state having the olefin in a psuedoaxial position (**10**/Figure 3) relative to the transition state having the olefin in a psuedoequatorial position (**9**).

Scheme 4



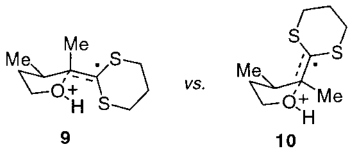
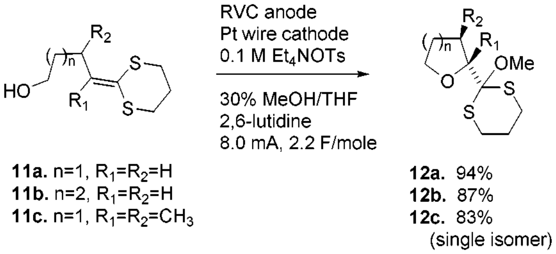


Figure 3. Two transition states for the cyclization of **11c**.

Substrates for addressing the compatibility of the ketene dithioacetal derived cyclizations with oxygen nucleophiles were synthesized by treating the corresponding lactone with trimethylaluminum and 1,3-propanedithiol in dichloromethane.[12] In the cyclization reactions that followed, the oxygen nucleophiles proved to be very effective traps for the ketene acetal based radical cations (Scheme 5). Using electrolysis conditions identical to those described above, both five- (**12a**) and six-membered ring (**12b**) ether products were obtained in high yield. The cyclization of **11a** was also accomplished with the use of a 6-V lantern battery as a power supply.[9b] This reaction led to an 86% isolated yield of the product, demonstrating that specialized equipment was not required for the cyclizations.

Scheme 5



The issue of stereochemistry was addressed by studying the cyclization chemistry of **11c**. In this case, the anodic oxidation led to an 83% isolated yield of *a single cyclized product* having the desired stereochemistry for the synthesis of (+)-nemorensic acid. A NOESY experiment was used to assign the stereochemistry of the product obtained. To this end, the methine proton at C_3 was used to establish the stereochemistry of the C_4 methylene protons. Only one of the C_4 methylene protons showed a strong interaction to the

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[10] For comparison purposes, the coupling of a trimethylsilyl-substituted enol ether derived ketene acetal equivalent with an enol ether terminating group also led to predominately cis products.[3a]

[11] For asymmetric syntheses of (+)-nemorensic acid, see: (a) Honda, T.; Ishikawa, F. *J. Org. Chem.* **1999**, *64*, 5542. (b) Dillon, M. P.; Lee, N. C.; Stappenbeck, F.; White, J. D. *J. Chem. Soc, Chem. Commun.* **1995**, 1645. For a racemic synthesis of nemorensic acid, see: (c) Klein, L. L. *J. Am. Chem. Soc.* **1985**, *107*, 2573.

[12] (a) Chamberlin, A. R.; Nguyen, G. D.; Chung, J. Y. L. *J. Org. Chem.* **1984**, *49*, 1682. (b) Corey, E. J.; Beames, J. D. *J. Am. Chem. Soc.* **1973**, *95*, 5829.

[13] For a comparison of enol ether and allylsilane trapping groups, see: Tinao-Wooldridge, L. V.; Moeller, K. D.; Hudson, C. M. *J. Org. Chem.* **1994**, *59*, 2381 along with ref 3b. For a comparison of allylsilane and alcohol trapping groups, see ref 3a.

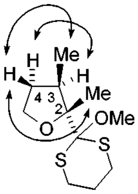
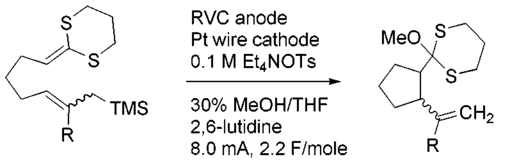


Figure 4. Key NOE interactions in compound **12c**.

C_3 methine (Figure 4). An NOE interaction between the C_4 methylene proton on the β-face of the molecule and both methyl groups then established the stereochemistry of C_2 as having the methyl group on the β-face of the molecule cis to the methyl at C_3. Clearly, the use of the ketene dithioacetal group increased the preference for the radical cation moiety to occupy a psuedoequatorial position in the transition state for the cyclization (Figure 3).

Finally, we turned our attention toward probing the compatibility of using ketene dithioacetal initiating groups with less reactive radical cation trapping moieties. To this end, the reactions using allylsilane terminating groups were studied (Scheme 6). While allylsilanes can be very effective trapping groups for enol ether radical cations, they are significantly less reactive than either enol ether or alcohol trapping groups.[13] In this case, the use of the less reactive trapping group did interfere with the cyclizations. While a moderate level of success was obtained using a disubstituted allylsilane trapping group (**13a**), the use of a trisubstituted allylsilane led to a messy reaction and only about a 20−30% yield of the product. The yield for this reaction was approximated by proton NMR because the product could not be isolated as a pure compound. At this time, it is not known why the trisubstituted allylsilane was a less effective trapping group than the disubstituted allylsilane.

Scheme 6



13a. R=H
13b. R=CH_3

14a. 55%
14b. (20-30%)

In conclusion, we have found that oxidative cyclization reactions can be effectively initiated by the anodic electrolysis of ketene dithioacetal groups. The reactions work well with both enol ether and oxygen trapping groups in order to form five- and six-membered ring products. Both types of cyclization reactions were found to be compatible with the generation of quaternary carbons, and both sets of reactions led to significantly higher levels of stereoselectivity than analogous reactions initiated by the oxidation of an enol ether. Efforts to utilize the reactions in total synthesis efforts are underway.

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Supporting Information Available: A sample experimental for the electrochemical procedure and characterization data for the electrochemical substrates and corresponding products is included along with copies of the proton NMR spectra and the NOESY data for **6a**, **6b**, and **12c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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