J|A|C|S
COMMUNICATIONS

Published on Web 07/20/2002

Anodic Cyclization Reactions: Capitalizing on an Intramolecular Electron Transfer to Trigger the Synthesis of a Key Tetrahydropyran Building Block

Shengquan Duan and Kevin D. Moeller*

Department of Chemistry, Washington University, St. Louis, Missouri 63130

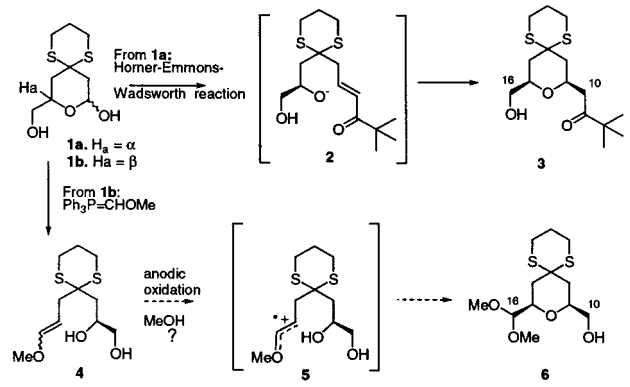
Received June 7, 2002

While the use of oxidation potentials can provide a guide for what will happen in a preparative oxidation reaction, their use can also be misleading. For example, we have found that in certain situations amides can be oxidized in the presence of electron-rich aromatic rings that have oxidation potentials over 300 mV lower than that of the amide.[1] In these cases, the initial oxidation of the aromatic ring leads to a rapid equilibrium between the radical cation of the aromatic ring and the radical cation of the amide. Product formation is then determined by which radical cation "decomposes" fastest under the reaction conditions, a scenario that fits the Curtin−Hammet principle.

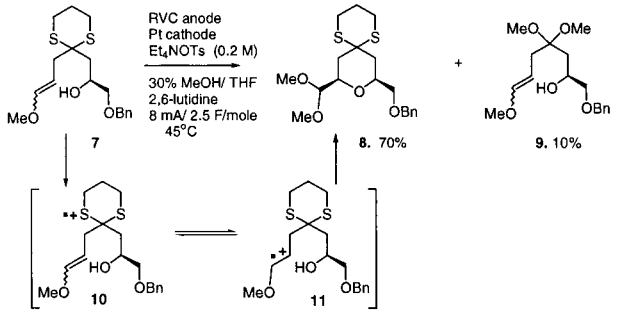
Yet how general was this observation, and was it dependent on the presence of the aromatic ring?[2] Recently, we began to wonder about these questions in the context of the chemistry outlined in Scheme 1. The sequential Horner−Emmons−Wadsworth/ Michael reaction strategy used by Vandewalle and co-workers to convert lactol **1a** into the tetrahyropyran **3** is one of the most efficient syntheses of a building block for the $C_{10}-C_{16}$ region of bryostatin reported to date.[3,4] Yet while the Vandewalle approach is very efficient (a total of only five steps), it has not been routinely employed in bryostatin syntheses.[5] Instead, the most successful bryostatin syntheses utilized a building block for the $C_{10}-C_{16}$ region that had an aldehyde at C_{16} and a protected alcohol at C_{10}.[5b] Alternative approaches used closely related building blocks that had protected alcohols at both the C_{16} and the C_{10} positions.[5a,c,d] Relative to these examples, building block **3** had extra carbons at the C_{10} terminus. These extra carbons were a consequence of the Michael reaction used by Vandewalle and co-workers to construct the tetrahydropyran ring. This Michael reaction required the addition of the ring oxygen to a carbon that was β to a carbonyl. However, the recent discovery that anodic oxidation reactions can be used to initiate cyclizations between enol ethers and alcohol nucleophiles[6] would suggest that the very efficient synthetic route pioneered by Vandewalle and co-workers might also prove useful for constructing $C_{10}-C_{16}$ building blocks that do not have the extra carbons found in **3**. As illustrated in Scheme 1, replacement of the Michael reaction in the Vandewalle approach with an anodic cyclization reaction would, in principle, enable the rapid conversion of lactol **1b** into a $C_{10}-C_{16}$ building block (**6**) having both the desired aldehyde equivalent at C_{16} and the alcohol at C_{10} already in place.

A cursory look at oxidation potentials would suggest that this proposal was seriously flawed. Methoxy enol ethers oxidize at a potential of +1.40 V versus a Ag/AgCl reference electrode.[7] The thioacetal (which played an important role in the synthesis of **3**) oxidizes at a potential of +1.16 V versus a Ag/AgCl reference electrode.[8] Therefore, the anodic oxidation of **4** would be expected to oxidize the thioacetal in preference to the enol ether. Yet would this really stop the cyclization reaction from occurring? In this case, the initially generated sulfur radical cation would "decompose" via

Scheme 1



Scheme 2



an intermolecular trapping reaction involving the methanol solvent. Because the specific adsorption of an electrolyte on the surface of the electrode can exclude solvent from the region surrounding the electrode and thereby impede solvent trapping of the reactive intermediates generated at the surface,[9] this reaction would potentially be slow relative to the intramolecular trapping reaction of an enol ether radical cation (**5**). If an intramolecular electron transfer between a sulfur radical cation and the enol ether were possible,[10] then a Curtin−Hammet type scenario might again control product formation in this reaction (Scheme 2).

To test this idea, electrolysis substrate **7** was synthesized[11] and then oxidized in an undivided cell using a reticulated vitreous carbon anode, a platinum cathode, a 0.2 M Et_4NOTs in 30% MeOH/THF electrolyte solution, and 2,6-lutidine as a proton scavenger. The reaction was performed at 45 °C with a constant current of 8 mA until 2.5 F/mol of charge was passed (Scheme 2). A 70% yield of the desired cyclized product was obtained, although the oxidation potential for **7** was measured to be +1.12 V versus a Ag/AgCl electrode. Approximately 10% of the product obtained from oxidation of the thioacetal group (**9**) was obtained.

The mechanistic proposal for the reaction was supported by two additional observations. First, the reaction benefited from the use of an elevated temperature (Table 1, entries 1−4). For example, when the reaction was run at room temperature, the yield of product

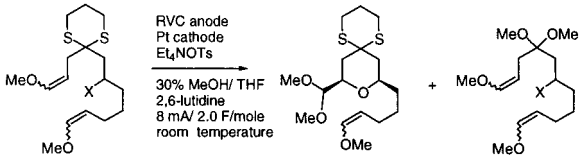
* To whom correspondence should be addressed. E-mail: moeller@wuchem.wustl.edu.

10.1021/ja027227+ CCC: $22.00

Table 1. Conditions for the Oxidation of Substrate **7**

entry	electrolyte	conc M	temp °C	recovered **7**	**8**	**9**
1	Et_4NOTs	0.2	−40	40%	0%	38%
2	Et_4NOTs	0.06	−20	10%	15%	20%
3	Et_4NOTs	0.2	room temp	0%	59%	≤10%
4	Et_4NOTs	0.2	+45	0%	70%	≤10%
5	Et_4NOTs	0.03	room temp	0%	54%	≤10%
6	Et_4NOTs	1.0	room temp	20%	49%	13%
7	$LiClO_4$	0.2	room temp	40%	0%	34%
8	Bu_4NBF_4	0.2	room temp	25%	20%	25%

Scheme 3



12a. X = H (41% recovered)
12b. X = OH

13a. Not applicable
13b. 52%

14a. 33%
14b. --

8 dropped to 59%. At −20 °C, a 15% yield of product was obtained (the change in electrolyte concentration for entry 2 would not be expected to have a large effect. For example, consider entries 3 and 5). At −40 °C, none of the desired product was formed. The inverse temperature effect on the yield of product was consistent with an intramolecular cyclization competing with an intermolecular side reaction. Because the intramolecular reaction pathway would involve a smaller entropy of activation, it would be favored to a greater extent over the intermolecular pathway as the temperature of the reaction increased. In each case, the formation of cyclized product **8** was accompanied by the formation of the intermolecular trapping product **9**. Unfortunately, product **9** proved difficult to isolate and unstable to the reaction conditions at room temperature and above. Therefore, its isolated yield did not provide an accurate indication of the course of the reaction, although it was clear that more of **9** did form in experiments where the yield of the cyclization reaction suffered. Second, the yield of cyclized product was sensitive to either the use of a high concentration of electrolyte (entry 6) or a change in the electrolyte employed (entries 7 and 8). These observations were again consistent with a cyclization reaction that was competing with an intermolecular trapping reaction. As mentioned earlier, the specific adsorption of an electrolyte on an electrode surface can protect the reactive intermediates generated at the electrode surface from solvent trapping. Changes in the concentration and nature of the electrolyte can significantly alter this situation and have a dramatic effect on the chemistry observed.[9b,12] The use of either a high concentration of electrolyte or a larger electrolyte (Bu_4NBF_4) can serve to reduce the extent of substrate coadsorption on the surface leading to greater exposure of the reactive intermediates generated to the solvent. The use of a smaller electrolyte ($LiClO_4$) can allow for a higher concentration of methanol to be present at the electrode surface. Both scenarios would lead to an increase in the rate of intermolecular trapping and a decrease in the yield of cyclized product.

Further evidence in support of the proposed intramolecular electron-transfer mechanism was gathered by examining the electrolyses of substrates **12a** and **12b** (Scheme 3).[11b] The oxidation of **12a** was performed to provide preparative support for the suggestion that it was the intramolecular cyclization reaction that "drove" the reaction toward the oxidation of the enol ether. In the absence of the trapping group, the anodic reaction led to oxidation of the thioacetal group and the formation of **14a**. An NMR spectrum of the crude reaction mixture showed no evidence for an oxidation of either enol ether. Reintroduction of the trapping group to the substrate (**12b**) then altered the course of the reaction to a point where it again led to a product derived from enol ether oxidation. In this case, a 52% isolated yield of the cyclized product **13b** was obtained. No evidence was found for oxidation of the second enol ether.[13] The selective oxidation of the enol ether proximal to the thioacetal in **12b** was clearly consistent with a mechanism that involved an initial oxidation of the thioacetal followed by an intramolecular electron transfer to form the enol ether radical cation that led to the cyclization. It would appear that the introduction of a thioacetal group into an electrolysis substrate allows for a new level of selectivity to be introduced into a subsequent anodic process.

In conclusion, an intramolecular electron-transfer reaction allows for the anodic coupling of an enol ether to an intramolecular oxygen nucleophile despite the presence of a thioacetal functional group that oxidizes at a lower potential than the enol ether. By taking advantage of this intramolecular electron transfer, the thioacetal group can be used to effect the selective oxidation of a proximal enol ether in the presence of an otherwise identical second enol ether.

Acknowledgment. We thank the National Science Foundation (CHE-9023698) for their generous support of this work. We also gratefully acknowledge the Washington University High Resolution NMR facility, partially supported by NIH grants RR02004, RR05018, and RR07155, and the Washington University Mass Spectrometry Resource Center, partially supported by NIHRR00954, for their assistance.

Supporting Information Available: A sample experimental for the electrochemical procedure, along with characterization data for the electrochemical substrates and corresponding products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Moeller, K. D.; Wang, P. W.; Tarazi, S.; Marzabadi, M. R.; Wong, P. L. *J. Org. Chem.* **1991**, *56*, 1058.
(2) For an intramolecular electron-transfer reaction involving a radical cation and a 4-methoxyphenyl ring as an electron donor, see: Chiba, K.; Miura, T.; Kim, S.; Kitano, Y.; Tada, M. *J. Am. Chem. Soc.* **2001**, *123*, 11314.
(3) De Brabander, J.; Vanhessche, K.; Vandewalle, M. *Tetrahedron Lett.* **1991**, *32*, 2821.
(4) For a review of synthetic efforts toward the Bryostatins prior to 1995, see: Norcross, R. D.; Paterson, I. *Chem. Rev.* **1995**, *95*, 2041.
(5) For alternate strategies, see: (a) Hale, K. J.; Hummersone, M. G.; Bhatia, G. S. *Org. Lett.* **2000**, *2*, 2189. (b) Evans, D. A.; Carter, P. H.; Carreira, E. M.; Charette, A. B.; Prunet, J. A.; Lautens, M. *J. Am. Chem. Soc.* **1999**, *121*, 7540. (c) Maguire, R. J.; Munt, S. P.; Thomas, E. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2853. (d) Lampe, T. F. J.; Horrmann, H. M. R. *Tetrahedron Lett.* **1996**, *37*, 7695.
(6) (a) Sutterer, A.; Moeller, K. D. *J. Am. Chem. Soc.* **2000**, *122*, 5636. (b) Duan, S.; Moeller, K. D. *Org. Lett.* **2001**, *3*, 2685. (c) Liu, B.; Moeller, K. D. *Tetrahedron Lett.* **2001**, *42*, 7163.
(7) Moeller, K. D.; Tinao, L. V. *J. Am. Chem. Soc.* **1992**, *114*, 1033.
(8) The $E_{p/2}$ value for the irreversible wave was measured using a Ag/AgCl reference electrode, a Pt anode, a 0.1 N $LiClO_4$ in CH_3CN electrolyte solution, and a sweep rate of 25 mV/s. These were the identical conditions used to measure the potential for the enol ether.
(9) (a) For general discussions of how the adsorption of a substrate and an electrolyte onto an electrode surface can exclude solvent and protect a reactive intermediate, see: *Organic Electrochemistry: Fourth Edition, Revised and Expanded*; Lund, H., Hemmerich, O., Eds.; Marcel Dekker: New York-Basel, 2001; p 802. *Synthetic Organic Electrochemistry*, 2nd ed.; Fry, A. J., Ed.; John Wiley and Sons: New York, 1989; p 126. (b) For a detailed example, see: Fry, A. J.; Reed, R. G. *J. Am. Chem. Soc.* **1972**, *94*, 8475.
(10) For the intramolecular oxidation of a carboxylate by a sulfur radical cation, see: Marciniak, B.; Hug, G. L.; Rozwadowski, J.; Bobrowski, K. *J. Am. Chem. Soc.* **1995**, *117*, 127.
(11) (a) Substrate **7** was synthesized from a lactol like **1b** that had the primary alcohol protected as a benzyl ether. The lactol was made using a modification (the protecting group was added in the first step) of the known procedure: Delorme, D.; Ducharme, D.; et al. *J. Med. Chem.* **1996**, *39*, 3951. (b) Substrates **12a**,**b** were assembled using variations on the dithiane chemistry used to construct **1b**.
(12) Missan, S. R.; Becker, E. I.; Meites, L. *J. Am. Chem. Soc.* **1961**, *83*, 58.
(13) The cyclized product was identified as having the thioacetal on the ring by using a TOCSY experiment to assign the connectivity of the molecule starting from the acetal methine proton.

JA027227+