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Oxidative Cyclization Reactions: Amide Trapping Groups and the Synthesis of Furanones

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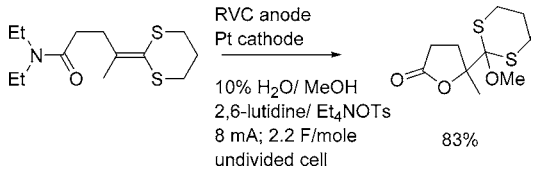
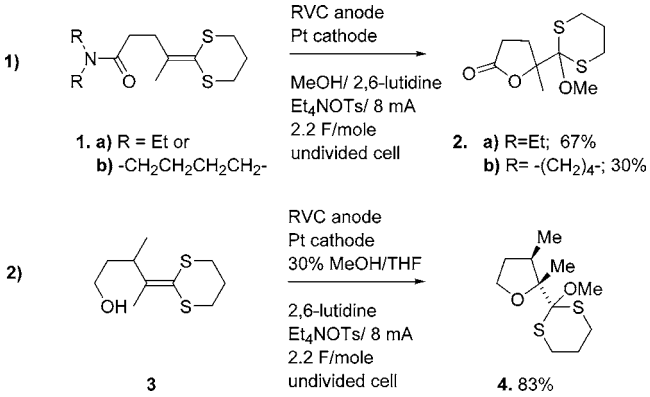
ABSTRACT



Intramolecular anodic coupling reactions involving ketene dithioacetal radical cations and amide trapping groups have been examined. The reactions generate furanone products and benefit greatly from the addition of water to the reaction medium. The cyclization reactions lead to products having stereochemistry that is directly analogous to oxidative cyclization reactions utilizing ketene dithioiacetal radical cations and alcohol trapping groups.

In connection with efforts to explore the synthetic utility of oxidative cyclization reactions,[1] we reported the anodic coupling of a ketene dithioacetal and an amide (Scheme 1, eq 1).[2] The discovery of this reaction suggested that oxidative cyclization reactions might provide a new route to the synthesis of the furanone and pyranone ring skeletons often found in natural products (Figure 1).[3−6] Such a strategy would be directly analogous to the very successful oxidative cyclization approach used in the synthesis of tetrahydrofuran derivatives.[7] However, two questions about the cyclizations needed to be addressed before any synthetic application of the reactions could be considered. First, the reaction illustrated in Scheme 1 was very sensitive to the nature of the amide group. The use of a diethylamine-derived amide led to a good yield of cyclized product, while the use of a pyrrolidine-derived amide led to a poor yield of cyclized product. Can the reaction conditions be modified so that a consistently high yield of product is formed? Second, the

Scheme 1



(1) For a review, see: Moeller, K. D. *Tetrahedron* **2000**, *56*, 9527.
(2) Liu, B.; Duan, S.; Sutterer, A. C.; Moeller, K. D. *J. Am. Chem. Soc.* **2002**, *124*, 10101.
(3) For the discovery of crobarbatic acid, see: Puri, S. C.; Sawhney, R. S.; Atal, C. K. *Experientia* **1973**, *29*, 390. For syntheses, see: Jang, D.-P.; Chang, J.-W.; Uang, B.-J *Org. Lett.* **2001**, *3*, 983 and references therein.
(4) For the discovery of integerrinecic acid lactone, see: Adams, R.; Van Duuren, B. L. *J. Am. Chem. Soc.* **1953**, *75*, 4631. For a recent synthesis, see: Honda, T.; Ishikawa, F.; Yamane, S. *J. Chem. Soc., Perkin Trans. 1* **1996**, *11*, 1125.
(5) For the discovery of incaninic acid, see: Yunusov, S. Y.; Plekhanov, N. V. *Dokl. Akad. Nauk USSR* **1957**, *5*, 13.
(6) For the discovery of butyrolactone I (kinase inhibitor), see: Kitagawa, M.; Okabe, T.; Ogino, H.; Matsumoto, H.; Suzuki-Takahashi, I.; Kokubo, T.; Higashi, H.; Saitoh, S.; Taya, Y.; Yasuda, H. *Oncogene* **1993**, *8*, 2425. For a recent biological study, see: Adona, P. R.; Leal, C. L. V. *Zygote* **2004**, *12*, 197.
(7) See ref 2, as well as: (a) Duan, S.; Moeller, K. D. *J. Am. Chem. Soc.* **2002**, *124*, 9368. (b) Duan, S.; Moeller, K. D. *Org. Lett.* **2001**, *3*, 2685. (c) Sun, Y.; Liu, B.; Kao, J.; d'Avignon, A.; Moeller, K. D. *Org. Lett.* **2001**, *3*, 1729. (d) Sutterer, A. C.; Moeller, K. D. *J. Am. Chem. Soc.* **2000**, *122*, 5636.

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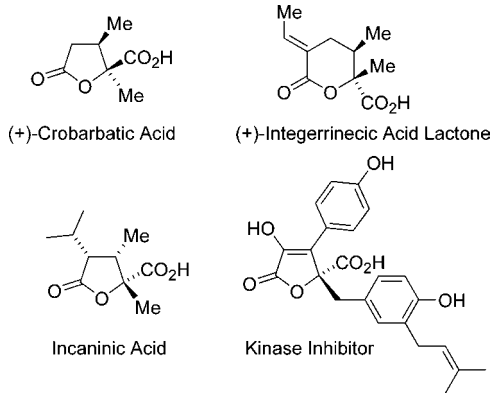


Figure 1.

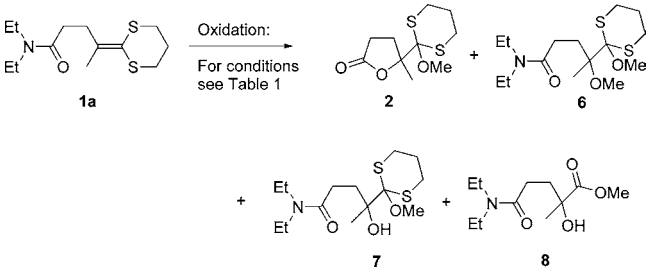
stereochemical preferences for the cyclization reaction were not known. Oxidative cyclizations using alcohol nucleophiles (Scheme 1, eq 2) lead to the formation of trans products when a stereogenic atom is placed next to the ketene dithioacetal.[2,7c] This stereochemistry results from a kinetically controlled reaction that is governed by both stereoelectronics and sterics. Do these same factors also govern the stereochemical outcome of oxidative cyclizations using amide nucleophiles?

With these two questions in mind, we undertook an effort to learn more about the mechanism of the reaction, develop optimal electrolysis conditions for the cyclizations, and determine the relative stereochemistry obtained for substrates with a stereogenic atom α to the ketene dithioacetal. We report here that cyclizations leading to furanone rings appear to be reversible and that they benefit greatly from the addition of water. The reactions favor the same stereochemical outcome as the reaction originating from the oxidation of **3**. However, the reversible nature of the cyclizations suggests that with an amide nucleophile, the stereochemistry of the product may be set by thermodynamics.

Our first goal was to increase the yield of the cyclizations. To this end, the conditions for the oxidation of substrate **1a** were systematically varied as summarized in Table 1. To establish a baseline, the original reaction conditions were repeated (entry 1). This experiment employed pure methanol solvent, tetraethylammonium tosylate as the electrolyte, a constant current of 8 mA, a reticulated vitreous carbon (RVC) anode, a Pt cathode, and an undivided cell. A 64% isolated yield of the cyclized product **2** was obtained along with 8% of the dimethoxylated product (**6**).

Initial attempts to improve the yield of the reaction examined solvent composition, electrolyte identity and concentration, electrode material, a divided vs undivided cell, and current density. None of these changes led to an improvement in the yield of the reaction, and at times they were detrimental. For example, adding a nucleophilically inert cosolvent to the reaction lowered the yield of the reaction. This observation was opposite to what is normally observed for anodic cyclization reactions. In most cases, anodic cyclizations benefit from the addition of a nonnucleophilic cosolvent that lowers the concentration of methanol and slows competitive solvent trapping of the initially generated radical cation.[8] The fact that lower concentrations of methanol hurt the reaction originating from **1a** suggests that in this case the relative rate of cyclization vs solvent trapping of the radical cation does not determine the product yield. An alternative explanation consistent with the need for a nucleophilic solvent would be that the yield of **2** is dependent upon the stability of cyclic intermediate **11** (Scheme 2). If **11** forms quickly but then undergoes an elimination reaction to form the very oxidizable **13**, then the

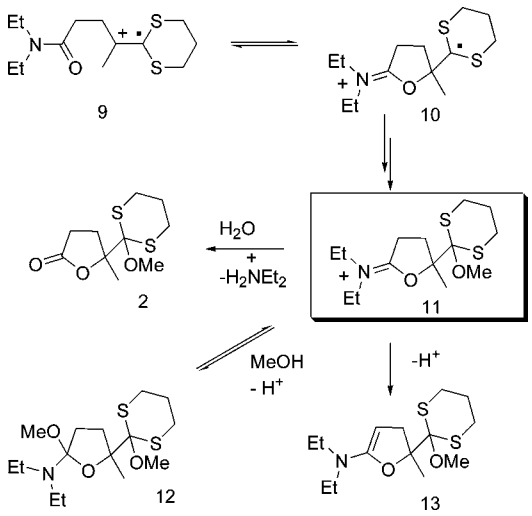
Table 1. Reaction Optimization



entry	conditions[a]	2	1a	6	7	8
1		64	1	8	0	0
2	10% H_2O, 2.2 F/mol	64	30	0	0	0
3	***10% H_2O, 3.0 F/mol***	***83***	***0***	***0***	***0***	***4***
4	1 g batch, 10% H_2O, 3.0 F/mol	78	0	0	0	0
5	2.5% H_2O, 3.0 F/mol	80	0	0	0	5
6	25% H_2O, 3.0 F/mol	69	0	0	0	3
7	pH buffered to ~9 (KH_2PO_4/Na_2HPO_4)	24	0	47	29	2
8	pH buffered to ~7.5 (TsOH/2,6-Lutidine)	6	0	11	19	4
9	3 equiv of Et_4NOTs/0.5 equiv of TsOH	3	0	34	12	0
10	anhydrous MeOH, 50 °C	29	0	50	0	0
11	10% water, 50 °C	45	0	3	6	2
12	rt anhydrous electrolysis, then 2 h at 50 °C	58	0	10	0	0

[a] Starting point for the reactions involved the use of a room temperature, constant-current electrolysis (8 mA) in an undivided cell with pure methanol as a solvent and Et_4NOTs as an electrolyte. A reticulated vitreous carbon anode and Pt cathode were used. The conditions listed indicate how the given experiments differed from these initial conditions.

Scheme 2



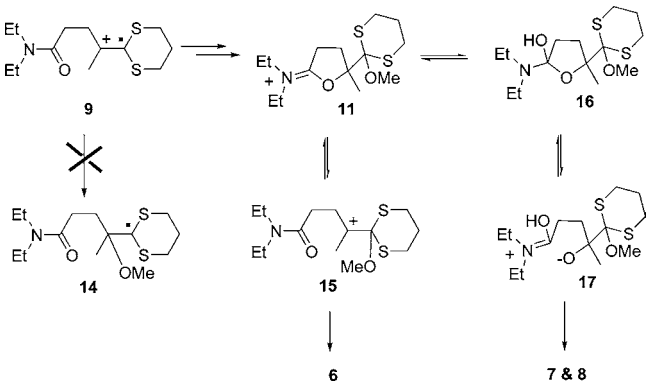
yield of the cyclization would be dramatically reduced by overoxidation. Trapping of **11** with a nucleophilic solvent would prevent the elimination and subsequent overoxidation. It was initially thought that **11** was trapped by the methanol solvent to form **12**, an intermediate that would persist in the reaction until hydrolysis either during workup or upon chromatography through silica gel. An attempt to verify the presence of intermediate **12** was made by carrying out the oxidation reaction in a d^4-methanol solvent along with lithium perchlorate as the electrolyte. In this way, the reaction could be examined by ^{1}H NMR without exposing the crude product to water. However, even without an aqueous workup, the lactone product **2** was formed, albeit in low yields (in this case the product contained a d^4-methanol-derived dithio ortho ester). Lactone **2** was presumably derived from trapping of **11** by adventitious water in the methanol solvent. Under no circumstances was the deuterated analogue of ortho ester intermediate **12** observed.

The absence of **12** in the crude product mixture suggested that iminium ion **11** persisted in solution even with a high concentration of methanol. This was most likely due to the reversibility of the methanol trapping step. With this in mind, the reaction conditions were altered in order to increase the rate of productive trapping of **11**. This was accomplished by adding water (10 vol %) to the electrolysis cell. In this case (Table 1, entry 2), the passage of 2.2 F/mol of charge through the cell containing substrate **1a** led to a cyclization that proceeded cleanly but did not go to completion. A 64% yield of the desired product **2** was formed along with 30% of the unreacted starting material. When the reaction was allowed to proceed until 3.0 F/mol of charge was passed, it afforded an 83% isolated yield of **2** with no remaining starting material (100 mg scale/Table 1, entry 3). When the scale of the reaction was increased to 1 g of substrate **1a** (entry 4), a 78% isolated yield of **2** was obtained. Under these conditions, the oxidation of the more problematic pyrrolidine-based substrate **1b** led to a 67% isolated yield of the lactone product **2b**. The reaction could not be optimized further by adding more water. Instead, higher concentrations of water lowered the yield of cyclized product (entry 6).

Several of the other attempts to raise the yield of the cyclization also deserve comment. For example, the decrease in current efficiency for the optimized experiments was attributed to the liberation of the secondary amine (either diethylamine or pyrrolidine) from the starting material. The oxidation potential for secondary amines range from approximately +0.8 to +1.1 V relative to a Ag/AgCl reference electrode. The oxidation potential for substrate **1a** was measured to be $E_{p/2} = +1.04$ V vs Ag/AgCl by cyclic voltammetry.[9] Thus, oxidation of the amine would compete with oxidation of the starting material at the anode. Efforts to increase the efficiency of the cyclization by lowering the pH of the reaction and protonating the amine led to significantly lower yields of cyclized product (Table 1, entries 7−9). Although the uncyclized products formed could not be isolated in pure form, HMBC NMR of the crude reaction mixture was most consistent with them being alcohols **7** and **8** (Table 1).

While it was tempting to suggest that the formation of **7** and **8** arose from trapping of the radical cation intermediate prior to cyclization, the amount of **7** and **8** generated renders this explanation unlikely. If the uncyclized products are generated from trapping of the radical cation prior to cyclization, then the ratio of alcohol to methyl ether product **6** should reflect the amount of water and methanol present in the reaction. In the experiments summarized in entries 7−9, 10% water was used. Given these experimental conditions, initial trapping of the radical cation intermediate before cyclization should lead to a 9:1 ratio of product **6** to products **7** and **8**. However, the experiments outlined in entries 7−9 led to substantially higher amounts of the alcohol product. In the experiment outlined in entry 8, the alcohol product was formed in preference to methyl ether **6**. Therefore, a more likely explanation for the formation of **7** and **8** is that they are generated from a pH-altered decomposition of cyclic intermediate **16** (Scheme 3). One can

Scheme 3



imagine such a change in mechanism being caused by protonation of the alkoxide in a transient open intermediate like **17**. This protonation would shift the equilibrium toward the uncyclized alcohol products.

Experiments performed at elevated temperatures suggest that product **6** might also arise from a cyclic intermediate. When a reaction using 100% methanol as a solvent was performed at 50 °C (entry 10), the reaction led to a 50% yield of **6** along with a 29% yield of lactone **2**. The addition of 10% water to this reaction (entry 11) led to a dramatic improvement in the yield of the cyclized lactone. The suppression of uncyclized products in this experiment with the addition of only 10% water was again not consistent with trapping of the initial radical cation intermediate before cyclization. Why would the addition of 10% water to the

(8) See for example: Hudson, C. M.; Marzabadi, M. R.; Moeller, K. D.; New, D. G. *J. Am. Chem. Soc.* **1991**, *113*, 7372. See also refs 2 and 5 above.

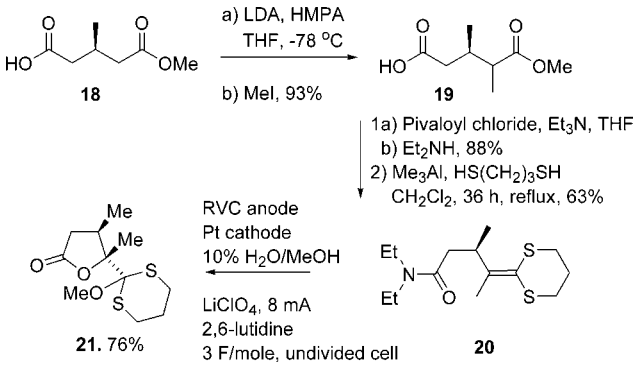
(9) Potentials were measured using Pt working and auxiliary electrodes, a Ag/AgCl reference electrode, a 0.1 M $LiClO_4$ in acetonitrile electrolyte solution, a sweep rate of 25 mV/sec, and a substrate concentration of 0.025 M. The reference electrode was calibrated using ferrocene as a standard.

solvent dramatically reduce the rate of methanol trapping of the radical cation? However, the presence of water in the reaction mixture would dramatically alter the fate of a cyclic iminium ion intermediate like **11** (Schemes 2 and 3). In the absence of water, methanol trapping of **11** would lead to the reversible formation of ortho ester **12** (Scheme 2). The iminium ion would eventually be converted to lactone product by trapping with adventitious water. Since the concentration of water in the reaction is low, the formation of lactone would be slow. At elevated temperatures, the rate of ring opening to the tertiary cation **15** (Scheme 3) would increase, providing an opportunity for the formation of **6**. The addition of water to the reaction would alter this scenario by increasing the rate of lactone formation, thereby decreasing the lifetime of **11**. It is interesting to note that the room-temperature reactions show the same suppression of product **6** when water is added to the reaction, albeit to a much smaller extent. Finally, an experiment (Table 1, entry 12) where the temperature of the anhydrous reaction was held at room temperature during the electrolysis and then raised to 50 °C for 2 h after the current was turned off led to an intermediate ratio of desired product **2** (68%) to uncyclized **6** (11%). Once the lactone is formed, it is not reopened to form the acyclic product upon heating.

The observations made above combine to suggest that intramolecular trapping of the initial radical cation is faster than solvent trapping but that an equilibrium exists between cyclic intermediates and acyclic intermediates during the course of the reaction. With this in mind, our current "working model" for the reactions is the one outlined in Schemes 2 and 3, although it should be noted that we have no data concerning the timing of steps in connection with the oxidation of the radical and subsequent trapping with methanol required for forming the dithioketal-based ortho ester. For example, one can readily imagine a scenario where oxidation of the radical is slow and does not occur until after the formation of a neutral radical. In this case, **10** would reopen to **9** in analogy to the radical solvolysis reactions reported by Crich and Newcomb[10] and the product distribution determined by the relative trapping of **10** by water and **9** by methanol.

Having established the best conditions for the cyclization, we turned our attention toward determining the stereochemical preferences for the reaction. To this end, substrate **20** was synthesized (Scheme 4). Oxidation of **20** using the optimized conditions led to the formation of a 76% isolated yield of product **21**. The stereochemistry of the product was

Scheme 4



determined using NOESY spectroscopy. The formation of the trans product indicated that the direction of selectivity for the cyclization was the same as that obtained for the analogous cyclizations leading to the formation of tetrahydrofurans.[2,7c] In this case, our mechanistic model for the reactions would suggest that the product was derived from either thermodynamic control or a kinetically controlled process in which water trapping of a cyclic intermediate was faster than reopening of the ring.

In conclusion, we have now answered both of the key questions required to begin utilizing oxidative cyclizations involving amide nucleophiles and ketene dithioacetal radical cations. First, a consistently high yield of cyclized product can be obtained from the reactions by adding water to the solvent mixture. Second, the product generated shows the same stereochemical preferences observed for previous oxidative cyclizations leading to tetrahydrofuran rings. This information will be vital in planning synthetic strategies that capitalize on oxidative routes to lactones.

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Supporting Information Available: Sample experimental procedure for the oxidation reaction, along with characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Please see: Horner, J. H.; Bagnol, L.; Newcomb, M. *J. Am. Chem. Soc.* **2004**, *126*, 14979 and references therein.