

Intramolecular Anodic Olefin Coupling Reactions: Using Competition Studies to Probe the Mechanism of Oxidative Cyclization Reactions

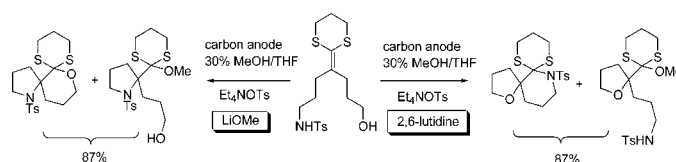
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ABSTRACT



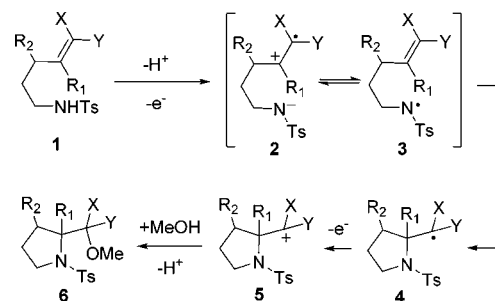
A competition experiment was designed so that the relative rates of anodic cyclization reactions under various electrolysis conditions can be determined. Reactions with ketene dithioacetal and enol ether-based substrates that use lithium methoxide as a base were shown to proceed through radical cation intermediates that were trapped by a sulfonamide anion. Results for the oxidative coupling of a vinyl sulfide with a sulfonamide anion using the same conditions were consistent with the reaction proceeding through a nitrogen-radical.

Radical cations derived from “enolate-equivalents” serve as interesting reactive intermediates for triggering a variety of new umpolung reactions.^{1–3} Yet while these reactions have shown significant synthetic potential, many mechanistic aspects of the transformations remain a mystery. For example, consider the coupling of ketene acetals and enoethers with toluene sulfonamides recently used to generate functionalized-proline derivatives (Scheme 1).^{4,5} The reactions benefit greatly from the use of basic reaction conditions, an observation that can be explained in one of two ways. Both would start with an initial deprotonation of the sulfonamide followed by an oxidation to generate a rapid equilibrium between intermediates **2** and **3**. The reaction would then proceed through either a transition state having a nitrogen anion adding to a radical cation or a transition

state having a nitrogen radical adding to an electron-rich olefin.⁶

In principle, these two pathways should be distinguishable. A reaction that proceeds through a transition state resembling **2** would involve a large change in polarity moving from the zwitterionic starting material to the neutral product. The transition state for the cyclization would be less polar than

Scheme 1. Anodic Coupling of Electron-rich Olefins and Toluene Sulfonamides



(1) For a review of nonoxidative approach to alkene radical cations see: Crich, D.; Brebion, F.; Suk, D. H. *Top. Curr. Chem.* **2006**, *263*, 1.

(2) For an alternative resulting from oxidation of an enamine see: Conrad, J. C.; Kong, J.; Laforteza, B. N.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2009**, *131*, 11640, and references therein.

(3) For a review of anodic oxidation approaches see: Moeller, K. D. *Synlett* **2009**, *8*, 1208.

(4) Xu, H.-C.; Moeller, K. D. *J. Am. Chem. Soc.* **2008**, *130*, 13542.

the starting material, and the reaction would be favored by the use of less polar solvents. A reaction that proceeds through a transition state resembling **3** would involve a neutral starting material and transition state. Such a reaction would not be as sensitive to changes in solvent polarity.⁷ Therefore, by varying the solvent polarity for the reaction it should be possible to determine which of the two pathways dominates the reaction mechanism. However, such a strategy for answering mechanistic questions about the reactions requires a method for determining if and how different reaction conditions alter the rate of the cyclization. In this paper, we illustrate how a competition study can be used to provide this information.

This work began by examining the oxidative-coupling of sulfonamides with a ketene dithioacetal group. To this end, substrate **7** was synthesized (Table 1).⁹ Since the trapping of a radical cation by an alcohol¹⁰ leads to a second, cyclic radical cation, the reaction leads to no net change in the charge of the transition state (Figure 1) for the reaction relative to the starting material. Hence, the rate of the alcohol-derived cyclization should be less sensitive to changes in solvent polarity than would be a reaction proceeding through a transition state resembling **2**. Hence, alcohol trapping of the radical cation should provide an effective “internal-standard” for probing how varying the reaction conditions for the electrolysis alters the rate of the nitrogen-based cyclization.

All of the anodic oxidation reactions utilizing substrate **7** were conducted using an RVC (Reticulated Vitreous Carbon) anode, a Pt-cathode, an undivided cell, and a constant current of 6 mA until 2.2 F were passed. In the first three oxidations (Table 1, entries 1–3), lithium methoxide was employed as a base and tetraethylammonium tosylate was used as the electrolyte. The three entries differed only in the solvent used

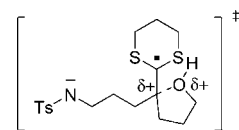


Figure 1. Trapping a radical cation by an alcohol.

for the reaction with the first using pure methanol, the second 60% MeOH/THF, and the third 30% MeOH/THF. When methanol was used as the solvent (entry 1), three products were generated. Two (**8a** and **8b**) were derived from a cyclization involving the toluene sulfonamide group. The third product (**8c**) was derived from alcohol trapping of the radical cation. The ratio of nitrogen trapping to oxygen trapping was 2.9:1. The oxidative cyclization was then repeated with increasing amounts of THF cosolvent to reduce the polarity of the reaction medium. When 60% MeOH/THF was used the ratio of nitrogen to oxygen trapping climbed to 12.7:1, and the yield of nitrogen trapping derived product climbed to 76%. With 30% MeOH/THF, none of the alcohol trapping product was observed, and an 87% isolated yield of nitrogen trapping product was obtained. Clearly, nitrogen trapping was favored by the less polar solvent supporting a radical cation type mechanism.

Table 1. Anodic Oxidation of **7**

entry	reaction conditions	8a + 8b		8c	8d
		(%)	8a,b/ 8c,d (%)		
1	MeOH 0.5 LiOMe, Et ₄ NOTs	58 (4.8/1) ^a	2.9/1	20	ND ^b
2	60% MeOH/THF 0.5 LiOMe, Et ₄ NOTs	76 (5.3/1)	12.7/1	6	ND
3	30% MeOH/ THF 0.5 LiOMe, Et ₄ NOTs	87 (4.1/1)	--	ND	ND
4	MeOH 0.5 LiOMe, LiClO ₄	50 (4.0/1)	1.8/1	27	ND
5	60% MeOH/THF 0.5 LiOMe, LiClO ₄	75 (4.8/1)	4.7/1	16	ND
6	30% MeOH/ THF 0.5 LiOMe, LiClO ₄	83 (5.9/1)	27.7/1	3	ND
7	30% MeOH/ THF lutidine, Et ₄ NOTs	ND	N.A.	39	17
8	30% MeOH/ THF lutidine, LiClO ₄	ND	N.A.	72	15

^a Numbers in the parentheses indicate the ration of **8a/8b**. ^b Not Detected.

The same trend was observed when lithium perchlorate was used as the electrolyte (Table 1, entries 4–6). The less

(5) For a review of cyclic amino acid derivatives see: Park, K.-H.; Kurth, M. J. *Tetrahedron* **2002**, *58*, 8629. (a) For recent references see: Mitsunaga, S.; Ohbayashi, T.; Sugiyama, S.; Saitou, T.; Tadokoro, M.; Satoh, T. *Tetrahedron: Asymmetry* **2009**, *20*, 1697. (b) Wang, Y.-G.; Mii, H.; Kano, T.; Maruoka, K. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3795. (c) Kaname, M.; Yamada, M.; Yoshifujii, S.; Sashida, H. *Chem. Pharm. Bull.* **2009**, *57*, 49. (d) Dickstein, J. S.; Fennie, M. W.; Norman, A. L.; Paulose, B. J.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 15794. (e) Prazeres, V. F. V.; Castedo, L.; Gonzalez-Bello, C. *Eur. J. Org. Chem.* **2008**, *23*, 3991. (f) Simila, S. T. M.; Martin, S. F. *Tetrahedron Lett.* **2008**, *49*, 4501. (g) Undheim, K. *Amino Acids* **2008**, *34*, 357, and references therein.

(6) For recent examples of amidyl radical cyclizations see: (a) Yuan, X.; Liu, K.; Li, C. *J. Org. Chem.* **2008**, *73*, 6166. (b) Sharp, L. A.; Zard, S. Z. *Org. Lett.* **2006**, *8*, 831. (c) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Barluenga, S.; Hunt, K. W.; Kranich, R.; Vega, J. *J. Am. Chem. Soc.* **2002**, *124*, 2233. (d) Stien, D.; Weinreb, S. M. *Tetrahedron Lett.* **2000**, *41*, 2333. (e) Clark, A. J.; Filik, R. P.; Peacock, J. L.; Thomas, G. H. *Synlett* **1999**, *4*, 441. (f) Clark, A. J.; Deeth, R. J.; Samuel, C. J.; Wongtap, H. *Synlett* **1999**, *4*, 444. (g) Horner, J. H.; Musa, O. M.; Bouvier, A.; Newcomb, M. *J. Am. Chem. Soc.* **1998**, *120*, 7738. (h) Esker, J. L.; Newcomb, M. *J. Org. Chem.* **1994**, *59*, 2779. (i) Esker, J. L.; Newcomb, M. *Tetrahedron Lett.* **1993**, *34*, 6877. (j) Esker, J. L.; Newcomb, M. *J. Org. Chem.* **1993**, *58*, 4933.

(7) Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*; Wiley-VCH: Weinheim, Germany, 2003.

(8) For previous chemical clock-type competition experiments for measuring the rate of an enol ether radical cation derived cyclizations see: (a) Horner, J. H.; Newcomb, M. *J. Am. Chem. Soc.* **2001**, *123*, 4364. (b) Horner, J. H.; Taxil, E.; Newcomb, M. *J. Am. Chem. Soc.* **2002**, *124*, 5402.

(9) Please see the supporting information for synthetic details.

(10) (a) Xu, H.-C.; Brandt, J. D.; Moeller, K. D. *Tetrahedron Lett.* **2008**, *49*, 3868. (b) Liu, B.; Duan, S.; Sutterer, A. C.; Moeller, K. D. *J. Am. Chem. Soc.* **2002**, *124*, 10101.

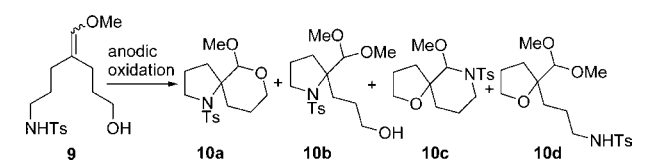
polar the medium, the more nitrogen trapping product observed. All of the reactions using lithium perchlorate as the electrolyte were less selective for nitrogen trapping than the corresponding reactions using tetraethylammonium tosylate as the electrolyte. This observation is consistent with the use of lithium perchlorate leading to a more polar reaction medium.

The competition study was also used to probe our initial premise that the yield of the nitrogen-based cyclizations improved when LiOMe was used as the base because it accelerates trapping of the radical cation by the sulfonamide relative to competitive solvent (methanol) trapping. When 2,6-lutidine is used in place of LiOMe as the base for the cyclization (Table 1, entries 7 and 8), only products from oxygen trapping of the radical cation are obtained. Clearly, the use of LiOMe accelerates the nitrogen-trapping reaction, presumably by deprotonating the sulfonamide prior to the oxidation in a manner inconsistent with the weaker 2,6-lutidine base.

With the success of the competition study for probing reactions using the ketene dithioacetal moiety, attention was turned toward probing similar reactions involving enol ether and vinylsulfide groups. For these efforts, substrates **9** and **11** were synthesized (Tables 2 and 3).⁹ In both cases, the oxidations were more selective for cyclizations involving the tosylamide trapping group than was the reaction triggered by the oxidation of **7**. This result is consistent with earlier findings that ketene dithioacetal derived radical cations undergo very efficient trapping reactions with alcohol nucleophiles.¹¹

With both the oxidation of **9** and **11**, no evidence of alcohol trapping could be observed when the less polar reaction conditions using tetraethylammonium tosylate as the electrolyte were utilized. Even when the more polar reaction conditions using lithium perchlorate were employed, alcohol trapping was only observed when the most polar solvent was chosen (Tables 2 and 3, entry 4). In the case of enol ether substrate **9**, the oxidation using the most polar set of conditions led to a 10% isolated yield of the alcohol trapping product along with a decreased amount of the nitrogen-trapping product. The use of a less polar solvent combination led to the disappearance of alcohol-trapping along with a corresponding increase in the yield of product derived from nitrogen-trapping (Table 2, entries 5 and 6). As with the ketene dithioacetal, this observation was consistent with the rate of nitrogen-trapping being favored by less polar solvents and therefore a mechanism that proceeded through a transition state resembling **2**. The low mass balance in the case of entry 4 appears to stem from a low yield of the oxygen trapping product once the pathway to that product becomes engaged. Evidence for this statement can be gathered from entries 7 and 8. In these experiments, the cyclizations are channeled toward alcohol trapping by removing the lithium methoxide and using 2,6-lutidine as the base. As in the earlier oxidation of the ketene dithioacetal and the oxidation of the vinylsulfide below, no product from nitrogen-trapping was observed in these experiments. However, unlike the other examples (entries 7 and 8 in Tables 1 and 3) the reactions could not be optimized to obtain an acceptable yield of

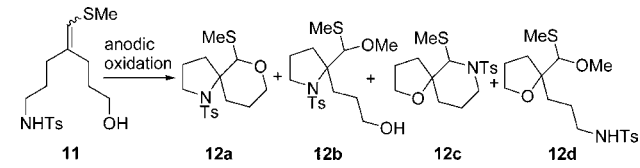
Table 2. Anodic Oxidation of **9**



entry	reaction conditions	10a + 10b (%)	10c (%)	10d (%)
1	MeOH 0.5 LiOMe, Et ₄ NOTs	83 (9.4/1) ^a	ND ^b	ND
2	60% MeOH/THF 0.5 LiOMe, Et ₄ NOTs	82 (4.1/1)	ND	ND
3	30% MeOH/ THF 0.5 LiOMe, Et ₄ NOTs	91 (3.6/1)	ND	ND
4	MeOH 0.5 LiOMe, LiClO ₄	48 (3.1/1)	ND	10
5	60% MeOH/THF 0.5 LiOMe, LiClO ₄	85 (3.5/1)	ND	ND
6	30% MeOH/ THF 0.5 LiOMe, LiClO ₄	79 (3.6/1)	ND	ND
7	30% MeOH/ THF lutidine, Et ₄ NOTs	ND	ND	27
8	30% MeOH/ THF lutidine, LiClO ₄	ND	ND	20

^a Numbers in the parentheses indicate the ratio of **10a/10b**. ^b Not Detected.

Table 3. Anodic Oxidation of **11**



entry	reaction conditions	12a + 12b (%)	12c (%)	12d (%)
1	MeOH 0.5 LiOMe, Et ₄ NOTs	88 (1/1.4) ^a	ND ^b	ND
2	60% MeOH/THF 0.5 LiOMe, Et ₄ NOTs	85 (1/1.6)	ND	ND
3	30% MeOH/ THF 0.5 LiOMe, Et ₄ NOTs	84 (1/2.1)	ND	ND
4	MeOH 0.5 LiOMe, LiClO ₄	82 (1/1.7)	ND	1–3
5	60% MeOH/THF 0.5 LiOMe, LiClO ₄	89 (1/2.8)	ND	ND
6	30% MeOH/ THF 0.5 LiOMe, LiClO ₄	92 (1/4.3)	ND	ND
7	30% MeOH/ THF lutidine, Et ₄ NOTs	ND	10	74
8	30% MeOH/ THF lutidine, LiClO ₄	ND	19	43

^a Numbers in the parentheses indicate the ratio of **12a/12b**. ^b Not Detected.

alcohol trapping product. The same should be true for the reaction run in entry 4.

The oxidation of **11** showed little dependence on the polarity of the solvent used. While a tiny amount of alcohol-trapping was seen when the most polar reaction conditions were employed (Table 3, entry 4), the yield of toluene sulfonamide coupling was consistently high for each of the reaction conditions attempted. This observation is more consistent with the vinylsulfide-derived cyclization proceeding through a nitrogen-radical type transition state resembling **3**. While the results are consistent with this suggestion, data using a competing reaction with a rate more closely matched to that of the toluene sulfonamide-derived cyclization is needed before a high level of confidence in this conclusion can be gained.

As in the earlier oxidation of **7**, the selective formation of the tetrahydrofuran derivatives from the oxidation of **11** could be realized in good yield by switching the base from LiOMe to 2,6-lutidine (Table 3, entries 7 and 8). In this case, the yield of product from alcohol-trapping could be raised to 84% when tetraethylammonium tosylate was used as the electrolyte for the reaction. For the oxidation of **11**, the expected products were obtained along with a small amount of **10c** (~1%) and **10d** (~3–4%) using either electrolyte. These products were formed by the oxidative methanolysis of **12c** and **12d**. Unpublished results from our group have shown that S,O-acetals are converted to dimethoxyacetals in good yields using the electrolysis conditions.¹²

(11) Huang, Y.; Moeller, K. D. *Tetrahedron* **2006**, *62*, 6536.

(12) For oxidations of dithioketals see: Porter, G. N.; Utley, J. H. P. *J. Chem. Soc., Perkin. Trans.* **1984**, *1*, 973.

In conclusion, the competition studies provide a valuable tool for probing the nature of oxidative cyclizations between electron-rich olefins and tosylamide nucleophiles. The studies show when a dithioketene acetal olefin is used in the reactions, the use of LiOMe as a base leads to a mechanism that can best be described as proceeding via the trapping of a radical cation by a sulfonamide anion. A similar result was obtained for an enol ether derived reaction, but the data obtained for a vinylsulfide derived reaction suggested a cyclization involving a nitrogen radical addition to an electron-rich olefin. Work to extend these studies to include competition-type probes for examining oxidative carbon–carbon bond forming reactions and for quantifying relative reaction rates for various trapping groups with a series of different radical cation intermediates are underway.

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Supporting Information Available: Detailed experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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