Anodic Cyclization

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Intramolecular Anodic Olefin Coupling Reactions: Use of the Reaction Rate To Control Substrate/Product Selectivity**

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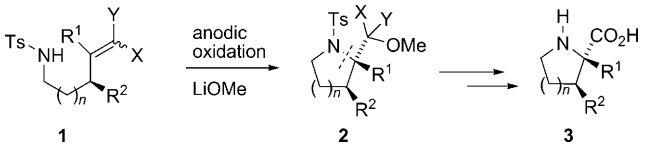
Anodic oxidation reactions can trigger a variety of interesting new cyclization reactions.[1] For example, the anodic coupling of an electron-rich olefin and a toluenesulfonamide leads to cyclic amino acid derivatives that contain tetrasubstituted carbon atoms (Scheme 1).[2,3] Such materials can potentially serve as building blocks for the construction of a variety of alkaloids and peptidomimetics.[4–8]

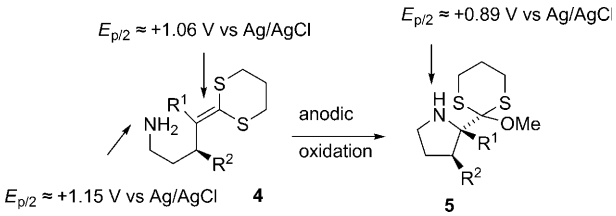


1 2 3

Scheme 1. Synthesis of cyclic amino acid derivatives containing tetrasubstituted α carbon atoms. Ts = *p*-toluenesulfonyl.

Enthusiasm for the use of this reaction in synthesis is enhanced by both the availability of the substrates in enantiomeric form[9] and the existence of a strategy for reversal of the configuration of the tetrasubstituted carbon atom generated.[10] It is dampened by the need for the sulfonyl protecting group and its subsequent removal.[11]

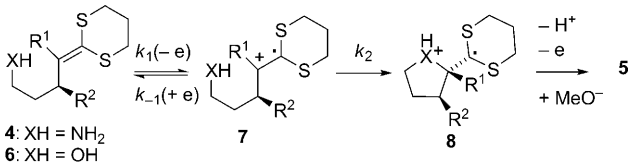
A potentially more useful approach would take advantage of an unprotected amine **4** as the nucleophile (Scheme 2).



Scheme 2. Proposed intramolecular anodic coupling of an amine and a dithioketene acetal.

However, although this reaction is easy to propose, the oxidation potentials highlighted in Scheme 2 provide reason for concern.[12] As illustrated, the reaction would employ a dithioketene acetal group as the electron-rich olefin for the oxidation. This group was selected because of its low oxidation potential. Even with this group, the oxidation potential of the secondary amine in the product is lower than that of either functional group in the starting material. This situation typically foreshadows overoxidation of the product. Hence, we protected the amine with a sulfonyl group to channel the oxidation toward the dithioketal and away from the amine in the product.

However, this analysis neglects the cyclization reaction and its possible influence on the oxidation potential of the substrate. Rapid cyclization reactions can lower the oxidation potential of a substrate.[13] For example, when the amine in **4** is replaced with an alcohol (**6** in Figure 1), the $E_{p/2}$ value of the substrate versus Ag/AgCl is 0.95 V:[12] a drop in potential from the isolated dithioketene acetal of 110 mV.



If "steady state", then...

$$[7] = \frac{k_1[\mathbf{4} \text{ or } \mathbf{6}]}{(k_{-1} + k_2)}$$

...and the Nernst equation becomes:

$$E_{obsv} = E^{o} - (RT/(nF)) \ln\left(\frac{[\mathbf{4} \text{ or } \mathbf{6}]}{[7]}\right)$$

$$E_{obsv} = E^{o} - (RT/(nF)) \ln\left(\frac{(k_{-1} + k_2)}{k_1}\right) \quad (1)$$

Figure 1. Relationship of observed potentials and cyclization rates.

This drop in potential can be explained on the basis of steady-state kinetics and the Nernst equation (Figure 1). In this treatment, steady-state kinetics is used to write an expression for the concentration of the radical cation **7**. This expression is then substituted into the Nernst equation to provide Equation (1). In this equation, E^{o} is positive, and everything following the minus sign is positive. Hence, as k_2 gets larger, and the cyclization faster, the observed potential decreases. One way to make k_2 larger would be to increase the nucleophilicity of the XH group, for example, by using an amine-based substrate, such as **4**. But how much does the

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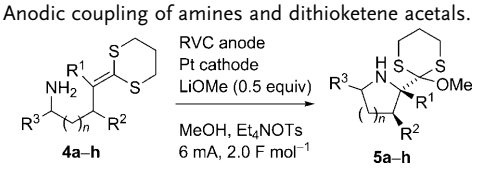
potential drop in this case, and is the potential drop large enough to make the potential of **4** lower than that of **5** so that the cyclization proposed in Scheme 2 might occur? We report herein that the potential drop is large enough, and that the sulfonyl protecting group in **1** was never needed.

Our investigation into the compatibility of amine trapping groups with anodic cyclizations began with the examination of a series of dithioketene acetal substrates (Table 1).[14] The first indication of how well the electrolyses would proceed came

Table 1: Anodic coupling of amines and dithioketene acetals.



Entry	4	n	R^1, R^2, R^3	$E_{p/2}$[a] [V]	Yield[b] [%]
1	**4a**	1	R^1 = Me R^2 = R^3 = H	0.60	84
2	**4b**	1	R^1 = R^2 = Me R^3 = H	0.62	81 (>20:1)
3	**4c**	1	R^1 = R^3 = Me R^2 = H	0.58	92[c] (3:2)
4	**4d**	1	R^1 = CH=CHMe R^2 = Me, R^3 = H	–	90 (10:1)
5	**4e**	2	R^1 = Me R^2 = R^3 = H	0.65	72
6	**4f**	2	R^1 = R^2 = Me R^3 = H	0.68	83[d] (10:1)
7	**4g**	2	R^1 = R^3 = Me R^2 = H	0.67	64[e] (2:1)
8	**4h**	3	R^1 = Me R^2 = R^3 = H	0.70	–

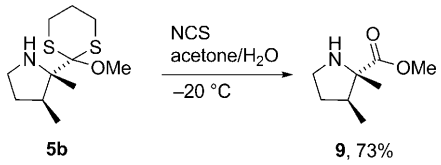
[a] The oxidation potential was measured versus Ag/AgCl on a carbon anode in acetonitrile. [b] The ratio in parenthesis is the diastereomeric ratio. [c] The product was obtained in 40% yield (measured by ^{1}H NMR spectroscopy by using an internal standard) when 2,6-lutidine (6 equiv) was used as the base instead of LiOMe. [d] Amount of current passed through the cell: 2.3 F mol^{-1}. [e] Amount of current passed through the cell: 2.4 F mol^{-1}.

when the oxidation potential for substrate **4a** (Table 1, entry 1) was measured to be $E_{p/2} = +0.60$ V versus Ag/AgCl:[12] a 460 mV drop in potential relative to an isolated dithioketene acetal. This drop in potential was the largest that we have measured to date. Clearly, the cyclization reaction with the more nucleophilic amine is very rapid.

The large drop in oxidation potential for **4a** led to a substrate potential that was approximately 300 mV lower than that of the product. Such molecules are readily differentiated in electrochemical oxidations. Accordingly, the preparative cyclization reaction led to the cyclic product in high yield. The oxidation was carried out by using an undivided cell, a reticulated-vitreous-carbon (RVC) anode, a platinum-wire cathode, an electrolyte solution composed of Et_4NOTs in MeOH, LiOMe (0.5 equiv) as a base, and a constant current of 6 mA until 2.0 F mol^{-1} of charge had been passed through the cell. Product **5a** was isolated in 84% yield.

A second substituent was added to the allylic carbon atom of the dithioketene acetal to probe the stereoselectivity of the reaction (Table 1, entry 2). Thus, substrate **4b** was subjected to the cyclization, and the product was isolated in 81% yield as a single diastereomer. The large orthoester in the product was found to be *trans* to the methyl group in position R^2 in analogy to earlier cyclizations with both sulfonamide[2] and oxygen[15] nucleophiles.

We converted the orthoester in product **5b** into a methyl ester to demonstrate how the cyclic products can be used to generate more traditional amino acid derivatives (Scheme 3). The reaction was carried out with *N*-chlorosuccinimide in an acetone/water mixture.[14]



Scheme 3. Hydrolysis of the electrolysis product **5b**.

The origin of the observed stereoselectivity in the formation of **5b** was attributed to a steric interaction between the methyl group in position R^2 and the larger substituent derived from the ketene dithioacetal. Evidence to support this suggestion was gathered by the oxidation of **4c** (Table 1, entry 3). In this case, the steric interaction was removed by moving the methyl group to position R^3. The cyclization proceeded in very good 92% yield, but led to a 3:2 ratio of diastereomers.

The need for LiOMe in the reactions was also probed with substrate **4c**. When LiOMe was replaced with 2,6-lutidine as a proton scavenger, the cyclization afforded the cyclic product in only 40% yield. The reaction led to a mixture of products. It was difficult to isolate **5c** in pure form, so the yield was determined by integration of the ^{1}H NMR spectrum of the product relative to an internal standard. There are two possible explanations for the decrease in the yield and cleanness of the reaction when LiOMe was not used as the base. First, it is possible that the use of the stronger base LiOMe leads to rapid deprotonation of the initial cyclic intermediate **8** (Figure 1). Rapid deprotonation would facilitate the cyclization by slowing down the reverse reaction. Second, it is possible that the use of methoxide accelerates trapping of the final cation generated by oxidation of the radical in **8** and thereby decreases the chance of secondary reactions taking place. The importance of efficiently trapping this cation has been demonstrated in previous cyclizations.[2,16]

The reactions are also compatible with the use of an unsaturated dithioketene acetal (Table 1, entry 4). The oxidation of **4d** led to the cyclic product in 90% yield as a 10:1 mixture of diastereomers. The major product was assigned as having the orthoester group *trans* to the methyl group in position R^2 in direct analogy to the corresponding example with an alcohol substrate.[10] The vinyl group was used because it offers an opportunity to manipulate the configuration of the tetrasubstituted carbon atom in the product. For example, a

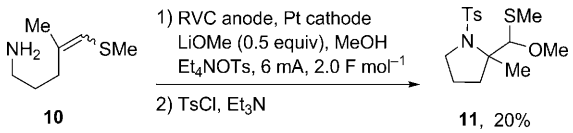
similar substitution pattern has been used to reverse the configuration of tetrasubstituted carbon atoms in tetrahydrofuran products.[10]

Following the success of the cyclizations to form five-membered rings, we wondered whether the amine was a good enough nucleophile to overcome the twin barriers of six-membered-ring formation and the generation of a tetrasubstituted carbon atom. If so, then the methodology would also enable the synthesis of pipecolic acid derivatives. Previous reactions in which a sulfonamide nucleophile was used for this purpose were only moderately successful, with an optimal yield of around 50% for the six-membered-ring products.

The use of the amine nucleophile for the synthesis of pipecolic acid derivatives proved to be quite efficient (Table 1, entries 5–7). The potentials measured for substrates **4e–g** were lower than that of the product (for the six-membered-ring product, $E_{p/2} = +0.95$ V versus Ag/AgCl), but not quite as low as those measured for the faster cyclizations to form five-membered rings. When substrate **4e** was oxidized, the six-membered-ring product was isolated in 72% yield. This cyclization proceeded much more efficiently than the corresponding cyclization with the toluene sulfonamide. When a substituent was placed on the allylic carbon atom of the dithioketene acetal (in **4f**), the cyclic product was formed in 83% yield as a 10:1 mixture of diastereomers. Once again, the stereoselectivity of the reaction was the result of steric interactions between the neighboring groups. When the methyl group was placed on the carbon atom bearing the amine nucleophile (substrate **4g**), the reaction led to the diastereomeric cyclic products in only a 2:1 ratio. The stereochemical mixture observed in this example suggests that the cyclizations proceed under kinetic control via an early transition state (without clearly defined equatorial and axial positions). This suggestion is consistent with the very fast cyclization.

Finally, we attempted to synthesize a seven-membered-ring analogue from substrate **4h** (Table 1, entry 8). Cyclic voltammetry for the substrate indicated a potential drop that was consistent with a rapid cyclization. However, none of the desired cyclic product was obtained from the preparative electrolysis of **4h**. Instead, a complex mixture of products was obtained. An ^{1}H NMR spectrum of this mixture indicated that substrate **4h** was consumed in the reaction. The spectrum showed no evidence of uncyclized products of elimination or methanol trapping (products typical of failed cyclization reactions). Hence, at this point we feel that the oxidation led to seven-membered-ring intermediates that were unstable under the reaction conditions.

Following the success of the cyclizations of dithioketene acetals, we wondered if the cyclizations were fast enough to enable the use of substrates with even higher oxidation potentials and examined the oxidation of the vinyl sulfide substrate **10** (Scheme 4). The oxidation potential for the vinyl sulfide in **10** is $E_{p/2} = +1.22$ V versus Ag/AgCl.[12] This value is significantly higher than the potential of the dithioketene acetal and in fact slightly higher than that of the primary amine. The cyclic voltammogram for **10** again showed a significant drop in potential relative to the oxidation potentials of the isolated functional groups (from 370 mV for the amine to $E_{p/2} = +0.78$ V versus Ag/AgCl).[17] The cyclization was again very fast, but the final potential reached suggested that the reaction might lead to competitive oxidation of the product ($E_{p/2} = +0.89$ V versus Ag/AgCl). In practice, this hypothesis turned out to be correct. In the oxidation of **10**, after the theoretical amount of current (2.0 F mol^{-1}) had been passed through the cell, the cyclized product was obtained in only 20% yield following its conversion into the toluene sulfonamide derivative **11**.[2] Starting material was also recovered in 17% yield, which indicated a decrease in the current efficiency of the reaction (an observation consistent with overoxidation of the product). The reaction gave a number of products, and isolation of the desired product before protection of the secondary amine was difficult. An attempt to completely convert the starting material into the product by passing 2.7 F mol^{-1} of current through the cell led to the isolation of no starting material or product. We concluded that, in this case, the drop in substrate potential was not enough to avoid complications with product oxidation.



Scheme 4. Anodic coupling of an amine and a vinyl sulfide.

In conclusion, a radical cation derived from a dithioketene acetal can be trapped by an unprotected amine. The reactions generate amino acid derivatives with a tetrasubstituted α carbon atom. At first glance, it appears that the reactions should fail as a result of the lower oxidation potential of the product relative to that of either of the functional groups in the starting material. However, such an analysis ignores the fact that the cyclization itself can lower the oxidation potential of the substrate. In the examples reported, the cyclizations are fast enough that the substrate potential is decreased to such an extent that it is significantly lower than that of the product. Clearly, the simple analysis of oxidation potentials for isolated functional groups can be very misleading in terms of the prediction of the success of an oxidative cyclization reaction. Studies to capitalize on the synthetic potential of the cyclization are underway.

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