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Anodic olefin coupling reactions involving ketene dithioacetals: evidence for a 'radical-type' cyclization

Yongmao Sun and Kevin D. Moeller*

Department of Chemistry, Washington University, St. Louis, MO 63130, USA

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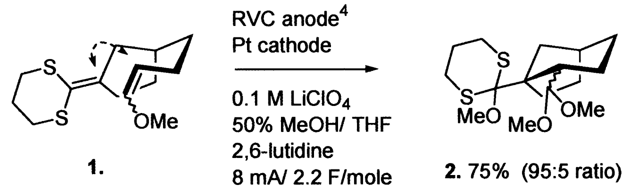
Abstract—A series of anodic coupling reactions between ketene dithioacetal groups and enol ethers have been studied in order to probe why some of the cyclizations are successful while other closely related attempts fail. It has been found that the success of the cyclization reactions strongly depends on the location of substituents on the olefins. The reactions are highly sensitive to substituents on the terminating olefin but not to substituents on the initial radical cation. This behavior is consistent with what has been observed previously with radical cyclization reactions. © 2002 Elsevier Science Ltd. All rights reserved.

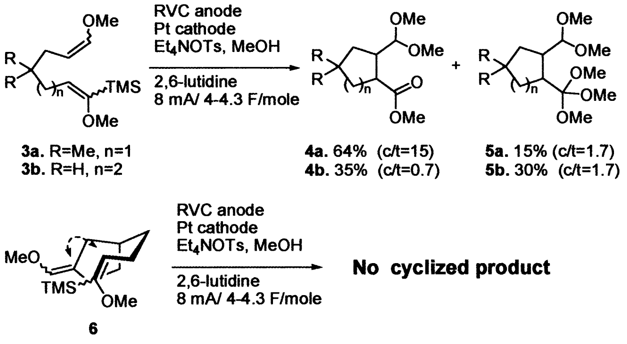
The anodic coupling of electron rich olefins can provide a powerful means for constructing carbon–carbon bonds.[1] Recently, we have shown that these reactions are compatible with the synthesis of bicyclo[3.2.1]octane ring skeletons.[2] The cyclizations appeared to be particularly useful when a ketene acetal equivalent was used as one of the olefin participants (Scheme 1).[3] In this way, the reaction led to a product having the ends of the cyclization already differentiated for further development.

Yet while the example illustrated in Scheme 1 proceeded very nicely, other apparently related cyclizations involving ketene acetal equivalents did not. For example, model studies had shown that silyl substituted enol ethers could serve as effective ketene acetal equivalents for anodic cyclization reactions (Scheme 2, substrates **3a** and **3b**).[2] However, the use of a silyl substituted enol ether as a participant in the formation of a bicyclo[3.2.1]octane ring skeleton (substrate **6**) led to none of the desired product. But why did this reaction fail?

There were two possible answers to this question. First, it was possible that the difference in the reactions resulting from the oxidation of **1** and **6** reflected an inherent difference in reactivity between the radical cation generated from oxidation of the ketene dithioacetal and the radical cation generated from oxidation of the silylated enol ether. Perhaps the presence of the silyl substituent lowered the reactivity of the radical cation to a point where it was no longer compatible with the formation of a quaternary carbon (the oxidation of a directly analogous bis enol ether substrate lacking the silyl group led to an 82% yield of the bicyclo[3.2.1]octane product).[2] Second, it was possible that the difference between the cyclizations reflected the location of the ketene acetal in the substrate. This second possibility was particularly intriguing because previous studies had shown that olefin coupling reactions involving enol ether derived radical cations pro-



Scheme 1.



Scheme 2.

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* Corresponding author. Tel.: 01-314-935-4270; fax: 01-314-935-4481; e-mail: moeller@wuchem.wustl.edu

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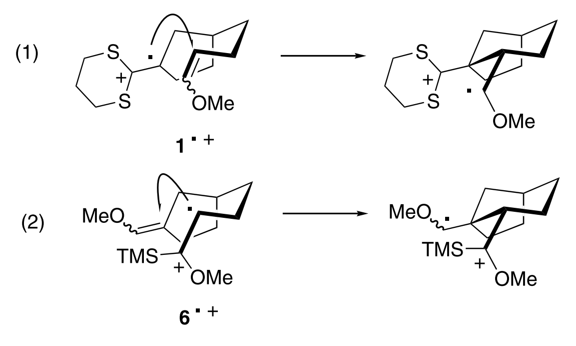
ceeded in a 'radical-like' fashion.[5,6] This meant that the radical cation attacked the trapping olefin in such a way as to form a radical intermediate at the terminating end of the cyclization. If the difference between the cyclizations originating from **1** and **6** did result from the location of the ketene acetal equivalent in the substrate, then the observations made would suggest that the same mechanism operated in the current reactions as well. The cyclization originating from substrate **1** would involve formation of a radical cation from the ketene acetal on the ring followed by a 6-*exo-trig* type cyclization onto a disubstituted enol ether (Scheme 3, Eq. (1)). The cyclization originating from substrate **6** would involve formation of a radical cation from the ketene acetal on the side chain followed by 6-*exo-trig* type cyclization onto a trisubstituted enol ether. In this case, the extra substituent would be on the internal carbon of the enol ether being attacked (Scheme 3, Eq. (2)). For radical cyclization reactions, such differences are significant. Radical reactions are generally not sensitive to the presence of substituents on the carbon bearing the initial radical (R_1 in Fig. 1). However, substituents on the internal carbon of the olefin being attacked (R_2 in Fig. 1) dramatically slow down the cyclizations.[7] Hence, if the radical cation reactions originating from the oxidation of **1** and **6** were 'radical-like', then the cyclization originating from **1** would be expected to proceed much better than the cyclization originating from **6**.

With this in mind, we set out to determine if the difference between the reactions originating from **1** and **6** was the result of either the location of the ketene acetal or the nature of the initiating group used. Since a substrate having a silylated enol ether on the ring proved difficult to synthesize, this effort focused on the synthesis and oxidation of a substrate having a ketene dithioacetal group on the sidechain (Scheme 4). In this sequence, the ketene dithioacetal group was introduced using the known Horner–Emmons–Wadsworth based procedure.[8]



Scheme 3.

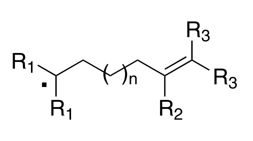
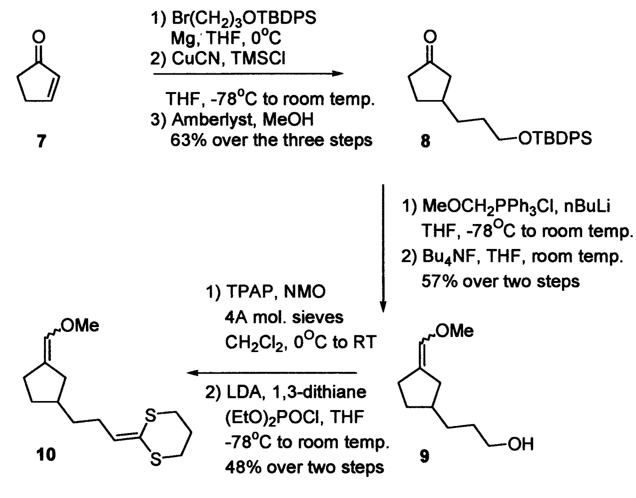


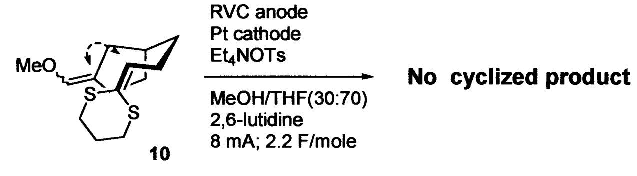
Figure 1.



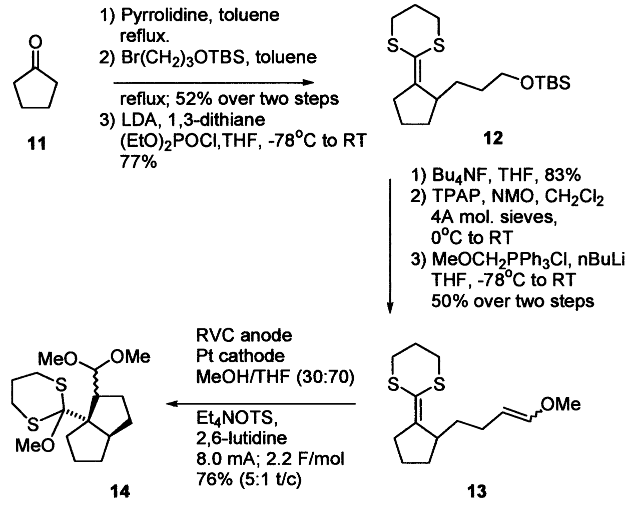
Scheme 4.

The oxidation of **10** was attempted using the same electrolysis conditions that had been used to successfully trigger the cyclization reaction from substrate **1**. In this case, the reaction led to a complex mixture of products. None of the desired cyclized product was obtained (Scheme 5). The 300 MHz ^{1}H NMR spectrum of the crude material did show that the enol ether group was intact in the product. Clearly, the ketene dithioacetal was oxidized but the cyclization did not occur. Based on this observation, it was apparent that the difficulties associated with the previous cyclization of **6** were not simply due to the use of the silylated enol ether ketene acetal equivalent, but rather resulted from the location of the ketene acetal initiating group.

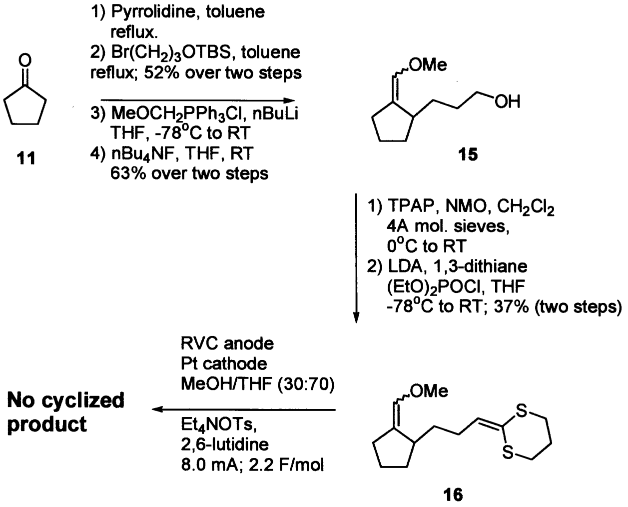
This observation was not restricted to cyclizations leading to bicyclo[3.2.1]octane ring skeletons. A pair of substrates that would afford fused bicyclo[3.3.0]octane ring skeletons upon cyclization were also studied. First, a substrate having the ketene acetal moiety on the ring (**13**) was synthesized and oxidized (Scheme 6). In this example, the oxidation led to a 76% isolated yield of cyclized product. The product had *cis* bridgehead stereochemistry and was obtained as a 5:1 ratio of stereoisomers about the newly formed bond. For comparison, a directly analogous substrate having the ketene dithioacetal on the side chain (**16**) was synthesized and oxidized (Scheme 7). As in the case of the oxidations leading to bridged bicyclic products, moving the ketene dithioacetal to the sidechain stopped the cyclization reaction from occurring.



Scheme 5.



Scheme 6.



Scheme 7.

In conclusion, it appears that anodic olefin coupling reactions that are triggered by the oxidation of a ketene dithioacetal functional group proceed in a 'radical-like' fashion. Like radical reactions, they are sensitive to steric hindrance on the internal carbon of olefin being attacked but not sensitive to steric groups on the carbon bearing the radical. This 'radical-like' behaviour is directly parallel to what has been observed for anodic cyclizations that are triggered by the oxidation of an alkyl enol ether, an observation that is critical for the design of future cyclization and tandem cyclization reactions that take advantage of ketene dithioacetals as initiating groups and olefins as trapping groups. It is important to note that this observation is dependent on the nature of the trapping group. Both cyclization reactions originating from the oxidation of a ketene dithioacetal and cyclization reactions originating from the oxidation of an alkyl enol ether show 'cation-like' behaviour when an alcohol nucleophile is employed as the trapping group.[9]

Acknowledgements

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