ORGANIC
LETTERS

2002
Vol. 4, No. 4
611−613

# Anion Radical Chain Cycloaddition of Tethered Enones: Intramolecular Cyclobutanation and Diels–Alder Cycloaddition

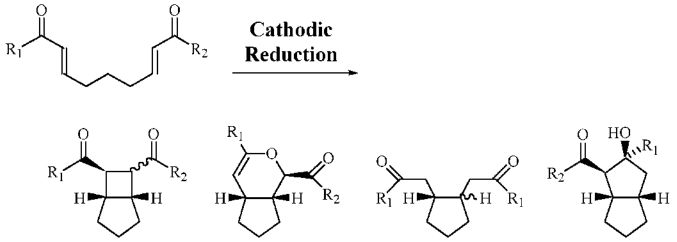
**Yeonsuk Roh, Hye-Young Jang, Vincent Lynch, Nathan L. Bauld,*,† and Michael J. Krische***

*Department of Chemistry and Biochemistry, The University of Texas at Austin, Austin, Texas 78712*

*mkrische@mail.utexas.edu*

**Received December 10, 2001**

## ABSTRACT



**The anion radicals of certain bis(enones), generated by cathodic reduction, are observed to participate in intramolecular cyclobutanation, yielding bicyclo[3.2.0]heptane derivatives through an anion radical chain mechanism. Evidence for stepwise cycloaddition involving distonic anion radical intermediates is presented. In addition to the novel anion radical cyclobutanations, an unprecedented intramolecular anion radical Diels–Alder product is observed. Parallel trends in substrate scope vis-à-vis the Co-catalyzed bis(enone) cyclobutanation are discussed.**

Recently, one of the present authors reported an intramolecular cobalt-catalyzed [2 + 2]cycloaddition of tethered enones.[1] Given the requirement of aroyl-substituted enone partners, the ease of reduction of the bis(enone) substrates and structural analogy to previously reported anion radical cyclobutanations,[2] it appeared reasonable to consider mechanisms invoking the intermediacy of anion radicals. To evaluate the plausibility of metal-catalyzed anion radical pathways and potentially expand the scope of these little known anion radical chain cycloadditions, the electrochemically promoted anion radical cycloadditions of several bis(enones) were investigated. Upon examination of a range of substrates, some parallel trends in the metal-catalyzed and electrochemically promoted processes are revealed.

Anion radical chain cycloadditions are of intrinsic interest. Whereas cation radical chain cycloadditions, including cyclobutanation, Diels−Alder cycloaddition, and cyclopropanation, are now well-known,[3] only two reports of anion radical chain cycloadditions are reported in the literature.[2] These studies describe the cyclobutanation of vinyl sulfone, vinylarene, and vinylheteroarene precursors. In both instances, cyclodimerization is proposed to occur through a chain mechanism involving the cycloaddition of a substrate anion radical to a neutral substrate molecule. Subsequent intermolecular electron transfer from the anion radical of the cyclized product to a neutral reactant molecule regenerates the substrate anion radical to propagate the chain. Here, we

---

† E-mail: bauld@mail.utexas.edu.

[1] Baik, T.-G.; Wang, L.-C.; Luiz, A.-L.; Krische, M. J. *J. Am. Chem. Soc.* **2001**, *123*, 6716.

[2] (a) Delaunay, J.; Mabon, G.; Orliac, A.; Simonet, J. *Tetrahedron Lett.* **1990**, *31*, 667. (b) Jannsen, R.; Motevalli, M.; Utley, J. H. P. *J. Chem. Soc., Chem. Commun.* **1998**, 539.

[3] Bauld, N. L. *Tetrahedron* **1989** *47*, 5307. Bauld, N. L. In *Electron Transfer in Chemistry*; Balzani, V., Ed.; Wiley-VCH: Weinheim, 2001; Vol. 2, p 133.

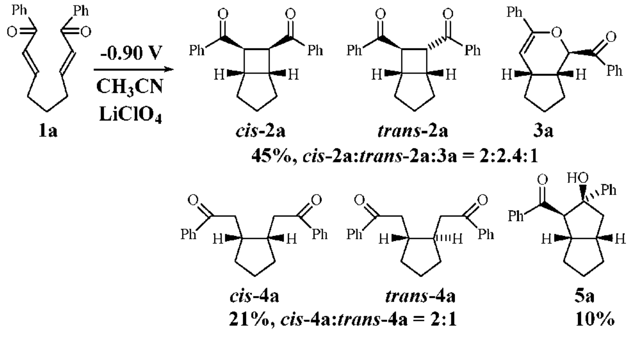
10.1021/ol0172065 CCC: $22.00

present evidence for a stepwise cycloaddition mechanism involving anion radical intermediates. In addition to products of cyclobutanation, an unprecedented intramolecular anion radical mediated Diels−Alder product is observed.

The substrate initially chosen for study was phenyl-substituted bis(enone) **1a**. Cyclic voltammetry revealed the peak reduction potential of **1a** to be −1.20 V versus SCE. Reduction was irreversible. To promote a chain process, reduction was carried out at a voltage (−0.90 V) well below that of the peak reduction potential using reticulated vitreous carbon working electrodes. It was subsequently verified that for reductions carried out at −1.50 V, essentially only dimerization and oligomerization result. Presumably, reduction at the lower voltage results in lower current densities and lower steady-state concentrations of the anion radical. Under these conditions, generation of bis(anion radical) intermediates is attenuated.

Given these considerations, a 0.02 M solution of **1a** in electrolyte solution (0.1 M $LiClO_4$ in acetonitrile) at ambient temperature was subjected to electrochemical reduction. The reduction was found to be essentially complete when only 30% of the theoretically required electrical charge had been passed, i.e., the starting material was completely consumed and the current had dropped to near zero. The overall yield of isolated products was 76%, with polymeric products accounting for the remaining mass balance. The products formed include the same bicyclic isomer *cis*-**2a** formed in the cobalt-catalyzed reaction, the corresponding stereoisomer *trans*-**2a**, and the unprecedented Diels−Alder cycloaddition product **3**. The total yield of these three bicyclic products is 45%, and the ratio of *cis*-**2**:*trans*-**2**:**3** is 2:2.4:1. In addition to these bicyclic products, the monocyclic product **4a** and the corresponding aldol product **5a** were formed in 21% and 10% yields, respectively. The structural assignment of **5a** was corroborated by X-ray crystallographic analysis (Scheme 1).

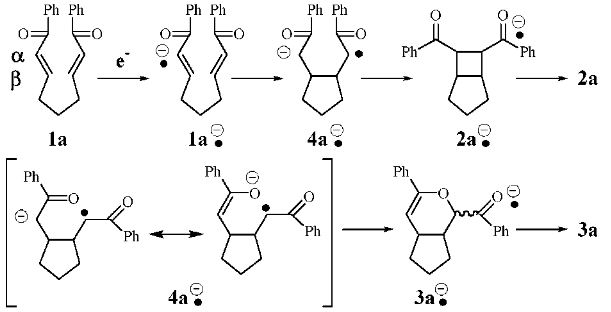
**Scheme 1.** Cathodic Reduction of **1a**



Since chain propagation requires an intermolecular electron transfer to neutral substrate, it appeared possible that increasing the initial concentration of **1a** would facilitate the chain process. Indeed, when the initial concentration of substrate was doubled (to 0.04 M), only 17% of the stoichiometrically required amount of electrical charge was required for the complete conversion of **1a**. However, the amount of dimeric and polymeric products increased to 52%.

The formation of both *cis*- and *trans*-**2a**, along with the monocyclic product **4a** (also a 2:1 mixture of *cis*/*trans* isomers), suggests a stepwise cycloaddition process involving the intermediacy of the distonic anion radical of **4a** formed via $\beta-\beta$ coupling of the monoenone monoanion radical of **1a**. The distonic anion radical of **4a** contains both enolate anion and enolyl radical moieties and is subject to α−α coupling to yield the anion radical of **2a**. This coupling is presumably made energetically feasible by the presence of the benzoyl moiety owing to delocalization of the incipient anion radical onto both the carbonyl and phenyl moieties. Chain propagation is achieved by an exergonic electron transfer from the anion radical of **2a** to neutral **1a**. For the anion radical of **4a**, coupling between the enolate oxygen and the α-carbon of the enolyl radical is also possible and gives rise to the formal hetero-Diels−Alder type adduct **3a**. Once again, a benzoyl group serves to stabilize the anion radical derived upon six-membered ring formation and exergonic electron transfer to starting material propagates the chain mechanism (Scheme 2).

**Scheme 2.** Postulated Stepwise Mechanism for Anion Radical Cyclobutanation



In addition to bicyclic products **2a** and **3a**, monocyclic product **4a** and related aldol product **5a** also are observed. These compounds are presumed to arise via protonation of the distonic anion radical of **4a**, followed by reduction of the remaining radical to an enolate anion and protonation of the latter. A portion of *cis*-**4** is then converted to the corresponding aldol addition product **5a**. The formation of both *cis*- and *trans*-**2a**, coupled with the formation of **4a**, provides evidence that the cycloadditions occur through a stepwise mechanism involving the anion radical of **4a**.

With regard to the mechanism of the cobalt-catalyzed cyclobutanation, parallel trends in substrate scope with respect to the electrochemically promoted reaction would lend support for a mechanism involving anion radical intermediates. In sharp contrast to the dibenzoyl enone **1a**, the corresponding bis(4-methoxybenzoyl) derivative **1b** does not undergo cyclobutanation in the presence of the $Co(dpm)_2$/silane catalysts system, instead favoring the Michael cycloreduction pathway.[4] In terms of a possible anion radical mechanism, the bis-anisoyl derivative **1b** should be more difficult to reduce than the parent benzoyl derivative **1a**. Under electrochemical conditions, generation of the anion radical of the bis(anisoyl) derivative **1b** should be possible, although a more negative potential should be required. The CV study of **1b** revealed a peak reduction potential at −1.30 V. Again, reduction was irreversible. The peak reduction potential of **1b** is ca. 0.1 V more negative than that of **1a**. Consequently, the reduction of **1b** was carried out at −1.0 V. *Reduction occurred under these conditions, and starting material was consumed, but no bicyclic products were formed*. Instead, dimers and oligomers of unknown structure and monocyclic products analogous to **4a** were observed. This suggests a likely explanation for the failure of **1b** to undergo cycloaddition: the formation of the second bond would require the anion radical moiety to reside upon an anisoyl moiety, which is less capable of stabilizing negative charge than a simple benzoyl group.

The CV study of the mixed anisoyl 4-nitrobenzoyl bis(enone) **1c** revealed a reduction potential of −1.00 versus SCE. Here, reduction was found to be reversible. Reversible reduction is attributed to the formation of a relatively long-lived anion radical, which is stabilized by the 4-nitrobenzoyl moiety. The reaction of this substrate was carried out at −0.8 V and failed to yield any bicyclic or monocyclic products, instead providing dimers and oligomers. Presumably, this relatively stable anion radical is unable to effect even the first bond formation. Reaction of this substrate in the presence of the Co(dpm)$_2$/silane catalysts system exclusively favors the cycloreduction pathway over cycloaddition. Finally, substrates **1d** and **1e** each fail to undergo intramolecular cycloaddition under cathodic reduction conditions or via cobalt catalysis (Figure 1).

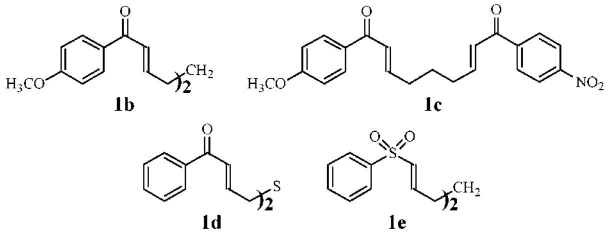
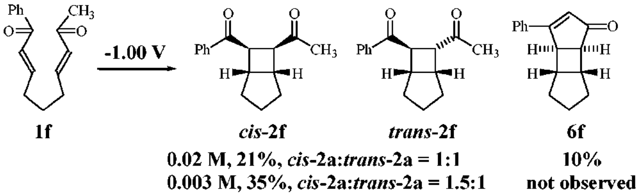


**Figure 1.** Additional bis(enone) substrates.

The key role of the benzoyl group in stabilizing the anion radical moiety of the product is evident from the mechanism depicted in Scheme 2. However, this mechanism does not require the presence of *two* benzoyl groups, suggesting that the mixed benzoyl/acetyl-substituted bis(enone) **1f** (peak reduction potential of −1.14 V) might be a suitable substrate for anion radical cyclobutanation. Upon cathodic reduction of **1f** at −1.0V at an initial concentration of 0.02 M, a 21% yield of bicyclic cyclobutanated products were obtained. Additionally, the tricyclic aldol−cyclodehydration product **6f**, characterized by single-crystal X-ray diffraction, was isolated in 10% yield. At lower concentration (0.003 M), the yield of **1f** is increased to 35% and tricycle **6f** is not observed. Interestingly, irrespective of concentration, no monocyclic products analogous to **4a** are detected. For **1f**, the observation of cycloaddition products under cathodic reduction parallels the result obtained in the cobalt-catalyzed reaction of **1f**, where the *cis*-*exo*-bicyclic product is formed exclusively in 63% yield (Scheme 3).

**Scheme 3.** Cathodic Reduction of **1f**



The present results provide new examples of a relatively uncommon reaction type, anion radical chain cyclobutanation. Furthermore, an example of a previously unprecedented anion radical chain Diels−Alder cycloaddition has been brought to light. As such, these studies provide a starting point from which the scope of these new reaction types may continue to broaden, as has proved to be the case for cation radical chain cycloadditions. With regard to the mechanism of the related cobalt-catalyzed reactions, substantial differences in stereoselectivity and the formation of products **3**−**6** render somewhat uncertain the assignment of a pure anion radical mechanism. However, these differences may arise from substantial changes in solvent polarity (acetonitrile vs 1,2-dichloroethane) and, most significantly, ion-pairing state in the two reaction types. Given the parallel trends in substrate scope, in particular the requirement of benzoyl-substituted enone partners, anion radical character of the cobalt-catalyzed reactions, which is significantly modulated by the presence of tightly ion-paired organocobalt species, cannot be excluded.

**Acknowledgment.** The authors thank the Robert A. Welch Foundation (F-149 and F-1466), the NSF-CAREER program, the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the CMC of UT Austin for partial support of this research.

**Supporting Information Available:** $^1$H NMR, $^{13}$C NMR, and HRMS data for all new compounds. X-ray crystallographic data for **5a** and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0172065

---

(4) Wang, L. C.; Jang, H.-Y.; Luiz, A. L.; Baik, T.-G.; Krische, M. J. Submitted.