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ELECTROLYTE-ASSISTED STEREOSELECTION AND CONTROL OF CYCLIZATION *vs* SATURATION IN ELECTROREDUCTIVE CYCLIZATIONS

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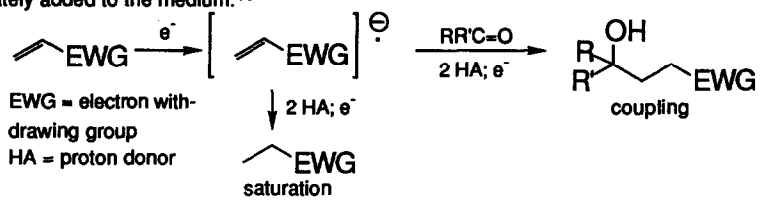
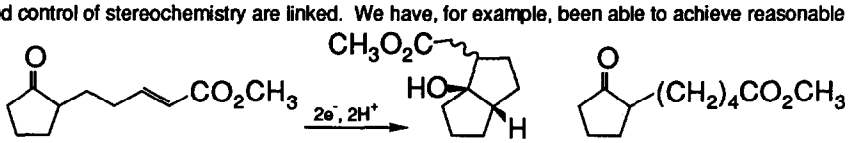
Abstract: The issues of C=C saturation *vs* cyclization and control of stereochemistry in the intramolecular electroreductive cyclization are discussed; guidelines for attaining selectivity are presented.

One persistent problem associated with the process of coupling a radical anion derived from an α,β-unsaturated ester or nitrile to a carbonyl compound or to another α,β-unsaturated ester or nitrile, is that saturation of the C=C pi bond can occur in competition with, or to the exclusion of coupling.[1] Saturation occurs when the β-carbon of the radical anion abstracts a proton from starting material or, as is usually the case, from a proton donor, HA (*e.g.*, dimethyl malonate), which has been deliberately added to the medium.[1d]



Another difficulty, which to a certain extent inhibits the widespread use of *electrochemical* methods, is that guidelines for achieving stereochemical control are not well established. In some respects, the issues of saturation *vs* cyclization and control of stereochemistry are linked. We have, for example, been able to achieve reasonable



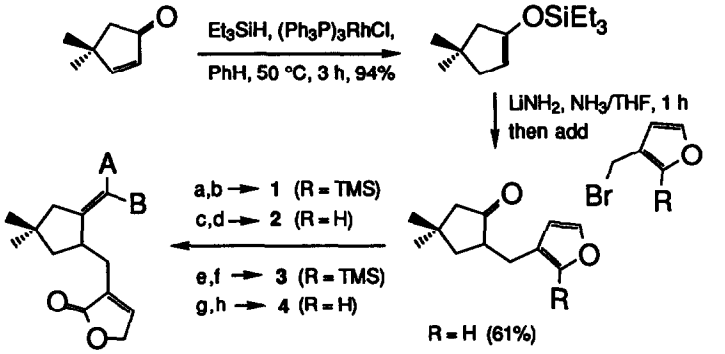
proton donor	ratio of *trans* to *cis* cyclized products[a]	percent C=C saturated product
$CH_2(CO_2C_2H_5)_2$	3.3:1	<2
$CH_2(CN)_2$	9:1	>80

a, The *cis*-product was isolated as the lactone; the terms *cis* and *trans* refer to the relationship between CH_2CO_2R and OR'.

stereochemical control in the electroreductive cyclization reaction illustrated above by increasing the acidity of the proton donor, but one also incurs significant amounts of saturation.[1d]

In this Letter, we address both issues, provide one solution to the first, and a guideline for achieving stereochemical control in electroreductive cyclizations.[1d]

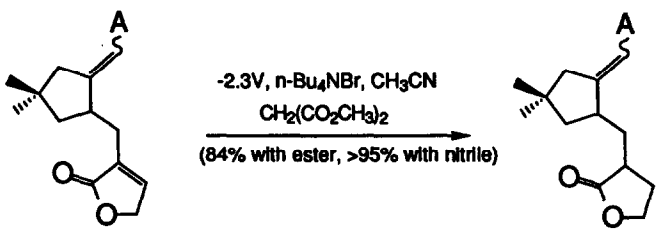
Two types of substrates were examined: those bearing a monoactivated alkene tethered to a butenolide, compounds **1** (mixture of E,Z-isomers) and **2** (E-isomer), and those doubly activated with either two ester or two nitrile groups, compounds **3** and **4**.[2] They were prepared in the straightforward manner illustrated below.[3]



1, A(B) = CO_2CH_3, B(A) = H
2, A = CN, B = H
3, A = B = $CO_2C_2H_5$
4, A = B = CN

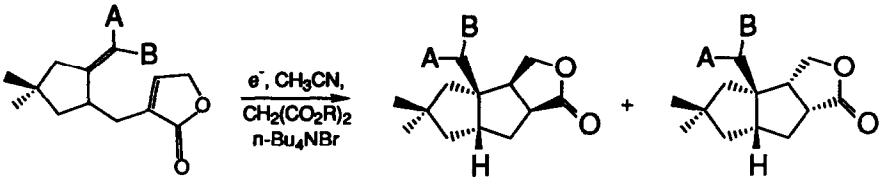
a, MCPBA, CH_2Cl_2/H_2O, 3-$ClC_6H_4CO_2Na$, 0 °C, 2 h, 46%; b, $(MeO)_2POCHNaCO_2Me$, THF, room temp, 26 h, 66%; c, $(EtO)_2POCHNaCN$, THF, room temp, 21 h, 93%; d, NBS, dioxane/H_2O (20:1), 0.5 h, room temp, 96%; e, $CH_2(CO_2Et)_2$, $TiCl_4$, pyr, 0 °C to room temp, 24 h, 18%; f, 30% aq AcOOH, AcONa, CH_2Cl_2, 4 h room temp, 96%; g, $H_2NCH_2CH_2CO_2H$, AcOH, $CH_2(CN)_2$, PhH, reflux, 12 h, 83%; h, NBS, dioxane/H_2O (20:1), room temp, 0.5 h, 48-72%.

Both the α,β-unsaturated monoester **1** and mononitrile **2** failed to cyclize; only saturation of the C=C pi bond of the butenolide was observed.



1, A = CO_2CH_3 (E,Z-mix)
2, A = CN (Z-isomer)
5, A = CO_2CH_3
6, A = CN

In dramatic contrast, both of the geminally activated systems **3** and **4** underwent cyclization, **3** → **7** and **8** (1:1 mixture, 90%) and **4** → **9** and **10** (1:1 mixture, 23% with 25% recovered starting material); saturation did not occur in either case.[4]



3, A = B = CO_2CH_3
4, A = B = CN

7, A = B = $CO_2C_2H_5$
9, A = B = CN

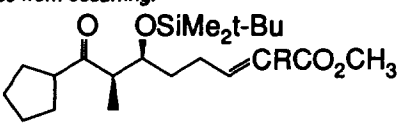
8, A = B = $CO_2C_2H_5$
10, A = B = CN

substrate	potential (V vs SCE; Hg pool cathode[a])	combined yield (%, 7+8 or 9+10)	product ratio (7:8 and 9:10)
3	-2.1	90	1:1
4	-1.6	23[b]	1:1

a, A Pt-foil anode was used in all cases. b, 25% recovered starting material, in this case.

The radical anions derived from **1** and **2**, being less delocalized than those derived from **3** or **4**, should be shorter lived and more reactive. We suspect, but have not proven, that they are also more basic, in the same way the carbanion derived from a monoester or nitrile is more basic than one derived from an alkylidene malonate or nitrile. If so, then the *kinetically preferred* pathway for **1**$^{\bullet-}$ and **2**$^{\bullet-}$ appears to be the proton abstraction which ultimately leads to saturation. The radical anions derived from **3** and **4**, being longer lived and less basic, are free to seek alternatives, including the observed cyclization.[5] The greater reactivity of **1**$^{\bullet-}$ and **2**$^{\bullet-}$ is reflected by an increase in the amount of saturated product produced, not by a more facile cyclization process.

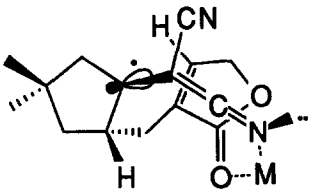
Based upon these results, we postulate: *If electroreductive cyclization is thwarted by preferential saturation of a carbon-carbon pi bond, then modify the substrate so that it possesses an electrophore which is activated geminally by electron withdrawing groups. A decrease in saturation, accompanied by a marked increase in cyclization is likely to be observed.* Unfortunately, this recipe does not provide a solution to all cases where the saturation/cyclization problem is encountered. For example, neither the mono- or the diactivated ketoester **11** or **12** undergo electroreductive cyclization onto the very hindered ketone carbonyl group; both lead efficiently to the product where the C=C pi bond has been saturated. A caveat, then, is that double activation will significantly improve the yield of cyclization *provided steric hindrance does not prevent the process from occurring.*



11, R = H
12, R = CO_2CH_3

Ideally, electroreductive cyclization should occur diastereoselectively; the reactions shown above do not. We have found that the stereochemical outcome is controlled by (at least) two closely related factors: the nature of the electrophore, and the choice of supporting electrolyte. For example, the reduction of simple α,β-unsaturated esters, ketones, aldehydes, *etc.*, requires the use of potentials more negative than -1.9 V, precluding the use of all but the most difficult to reduce supporting electrolytes; quaternary ammonium salts work well. Doubly activated substrates, on the other hand, are reduced at significantly more positive potentials (-1.6 to -1.7 V), thereby allowing selection from a much wider range of supporting electrolytes. This means that one can choose salts, such as LiX and MgX_2, where the metal is capable

of chelation to one or more heteroatoms in the substrate to be reduced, and/or in the radical anion formed after reduction. A *highly speculative* schematic illustrating this idea with a possible species *en route* to the *cis,anti,cis*-adduct **9**, is shown below.



In accord with these suggestions, we have found that reduction of bis-nitrile **4** in the presence of 0.1 M lithium perchlorate leads to a 3:1 mixture of the *cis,anti,cis* and *cis,syn,cis*-diastereomers **9** and **10**; an even higher 11.4:1 ratio is observed when 0.1 M magnesium perchlorate is used as the supporting electrolyte. That chelation between the proximal nitrile and one or both of the oxygen atoms of the butenolide is responsible for the stereoselectivity, is given credibility if one realizes that it drops to zero when a supporting electrolyte which is not capable of complexation, *viz.*, *n*-Bu_4NBr, is used under otherwise identical conditions. We intend to explore in greater detail the utility of using *chelation as a means of controlling stereochemistry in electrochemical reactions.*

potential (V, SCE)	supporting electrolyte	yield (%, **9** + **10**)	product ratio (**9**:**10**)
-1.7	$LiClO_4$	77	3:1
-1.6	$Mg(ClO_4)_2$	62	11.4:1

Acknowledgements. We are grateful to the National Science Foundation for supporting this research.

References and Notes

1. (a) *Organic Electrochemistry*, 2nd ed.; Baizer, M. M. and Lund, H., Eds.; Marcel Dekker: New York, 1983. (b) Little, R. D. and Baizer, M. M. In *The Chemistry of Enones;* Patai, S. and Rappoport, Z., Eds.; Wiley: New York, 1989; Chapter 14. (c) Baizer, M. M. *Chemtech*, **1980**, *10*, 161. (d) Little, R. D.; Fox, D. P.; Van Hijfte, L.; Dannecker, R.; Sowell, C. G.; Wolin, R. L.; Moëns, L.; Baizer, M. M. *J. Org. Chem.*, **1988**, *53*, 2287.

2. No indication of a reversible redox couple was observed in any instance, suggesting either that reduction and cyclization occur in concert, or that once reduction to the radical anion has occurred, a rapid follow-up reaction ensues (cyclization? protonation?), one which depletes the supply of the radical anion faster than it is oxidized.

3. (a) Exon, C.; Nobbs, M.; Magnus, P. *Tetrahedron*, **1981**, *37*, 4515. (b) Goldsmith, D.; Liotta, D.; Saindane, M.; Waykole, L.; Bowen, P. *Tetrahedron Lett.* **1983**, *24*, 5835. (c) Lehnert, W. *Tetrahedron*, **1973**, *29*, 635. (d) Prout, F. S. *J. Org. Chem.* **1953**, *18*, 928. (e) Kocienski, P. J.; Cernigliaro, G.; Feldstein, G. *J. Org. Chem.*, **1977**, *42*, 353.

4. Extensive decoupling and nOe experiments were performed to assist in establishing the structure of the products. For **9**: ^1H NMR (500 MHz. $CDCl_3$) δ 4.75 (dd, 1H, J = 11, 5), 4.52 (dd, 1H, J = 10.8, 7.8), 3.80 (s, 1H,), 3.25 (q, 1H, J = 8), 3.17 (td, 1H, J = 8.25, 5.0), 2.85 (qd, 1H, J = 7.8, 4.0), 2.30 (dt, 1H, J = 15, 7.5), 2.12 (ddd, J = 13.5, 9.0, 4.0), 2.00 (d, 1H, J = 14.7), 1.92 (dd, 1H, J = 13.5, 7.5), 1.85 (d, 1H, J = 15), 1.55 (dd, 1H, J = 13.5, 7.5), 1.18 (s, 3H), 1.14 (s, 3H). For **10**: δ 4.51 (dd, 1H, J = 10.5, 6), 4.38 (d, 1 H, J = 10.5), 3.81 (s, 1H), 3.25 (td, 1H, J = 9, 1), 3.02 (dd, 1H, J = 9, 6.5), 2.76 (q, 1H, J = 8.5), 2.36 (dt, 1H, J = 14, 9), 2.14 (d, 1H, J = 14), 1.84 (ddd, 1H, J = 13.5, 7.5, 1.5), 1.77 (d, 1H, J = 15), 1.67 (dd, 1H, J = 14.5, 1.5), 1.30 (dd, 1H, J = 13.5, 10.5), 1.11 (s, 3H), 1.07 (s, 3H).

5. We intend to use rapid scan and low temperature cyclic voltammetry coupled with electron spin resonance spectroscopy to study these concepts in greater detail.

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