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Insights into the Electrochemical Reductive Cyclization of α,β-Unsaturated Carbonyl Derivatives

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Summary: A series of acyclic and cyclic α,β-unsaturated esters bearing tethered mesylate leaving groups have been electrochemically reduced to give synthetically useful yields of monocyclic and bicyclic esters *via* attack of the β-carbon of the α,β-unsaturated ester on the carbon bearing the mesylated moiety.

Reductive cyclization reactions of α,β-unsaturated ketones with the β-carbon acting as a nucleophilic center have been known for over twenty years.[1] The conversion of **1** into **2** has been reported to occur in 45% yield *via* lithium in liquid ammonia reduction,[1] 96% yield *via* electron transfer from lithium dimethylcuprate,[2] and 98% yield *via* cathodic reduction.[3,4] Unfortunately, relatively little is known about the scope and mechanistic detail of this reaction. For instance, in certain cases it is assumed that an anion radical, generated by reduction of the α,β-unsaturated carbonyl compound, is the nucleophile,[3,4a,4c,4d] while in at least one case, it is proposed that a tethered halide is reduced to form a nucleophile which adds to the α,β-unsaturated carbonyl derivative in a Michael type addition.[4b] We now report a variety of studies which more clearly define the scope, limitations and mechanism of this potentially useful synthetic procedure.

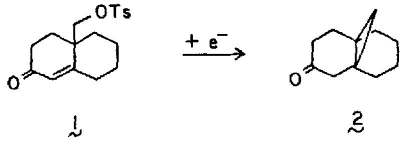
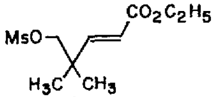
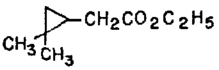
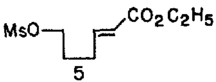
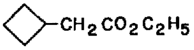
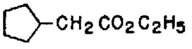
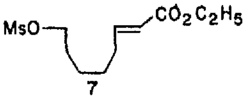
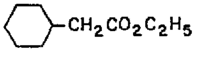
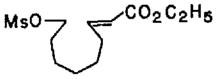
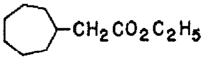


Table 1 lists the yields of expected cyclization products from the cathodic reduction[5,6] of acyclic α,β-unsaturated esters in both the absence and the presence of a proton source (dimethyl malonate, **3**). Examination of the yields obtained in the absence of a proton source indicates that the yields are a function of the rate of nucleophilic displacement of the mesylate anion by the electrochemically generated anion radical. The yields are ordered roughly in the order of the relative rates of intramolecular nucleophilic displacement.[7] This concept is supported by the observation that addition of dimethyl malonate, as a proton source, eliminates the cyclization process for **5**, **7**, and **8**, reduces the amount of cyclization in the case of **6**, and has little effect on the cyclization of **4**. This indicates that proton transfer from **3** to the anion radicals generated from **5**, **7**, and **8** is faster than cyclization, while proton transfer from **3** to the anion radical generated from **6** is competitive with cyclization. The yields of reduction products formed from **5**-**8** in the presence of **3** support this argument. The reductive cyclization of **4** was unaffected by the addition of **3**. This indicates that intramolecular displacement of the mesylate anion by the anion radical generated from **4** occurs faster than proton transfer from **3** to this anion radical.

Table 1. Yields of Anticipated Cyclization Products of Acyclic α,β-Unsaturated Esters in the Absence and Presence of Dimethyl Malonate (**3**, 2 Equivalents)[5]

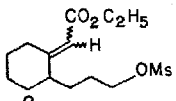
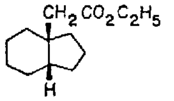
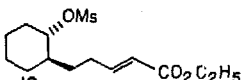
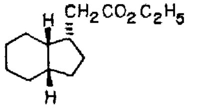
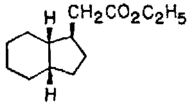
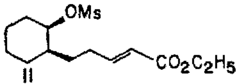
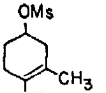
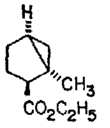
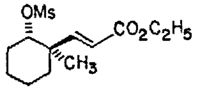
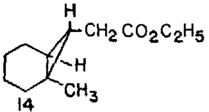
Substrate	Cyclization Product	Yield in the Absence of **3**	Yield in the Presence of **3**	Reduction Product Formed in the Presence of **3** (Yield)
 **4**		91%[a]	88%	--
 **5**		6%[b]	--	$MsO\text{-}(CH_2)_5\text{-}CO_2C_2H_5$ (65%)
 **6**		83%[a]	46%	$MsO\text{-}(CH_2)_6\text{-}CO_2C_2H_5$ (37%)
 **7**		58%[b]	--	$MsO\text{-}(CH_2)_7\text{-}CO_2C_2H_5$ (68%)
 **8**		4%[b]	--	$MsO\text{-}(CH_2)_8\text{-}CO_2C_2H_5$ (70%)

(a) Working potential = -2.2 V *vs* SCE. (b) Working potential = -2.3 V *vs* SCE.

For the reductive cyclization of **4**, it appears that electron transfer to the α,β-unsaturated ester may be the rate-determining step. Peak potentials (E_p) for cathodic reduction, as determined by cyclic voltammetry at a scan rate of 100 mV/sec at a Au-Hg plate electrode, showed the E_p for ethyl crotonate, **5**, **7**, and **8** to be -2.47 to -2.49 V. For **4** and **6**, the corresponding E_p values were -2.32 V and -2.41 V, respectively. These reduced E_p values can be associated with kinetic shifting of the reduction potentials due to rapid or concerted loss of the mesylate anion in the reductive cyclizations of **4** and **6**.

Reductive cyclizations of the type described above were not restricted to acyclic systems. Cyclic starting materials[8] should offer an advantage due to the decreased rotational freedom which the ring systems provide. Table 2 lists the results obtained in the reductive cyclizations of a series of α,β-unsaturated esters which have restricted rotation due to the incorporation of a ring into the linkage between the α,β-

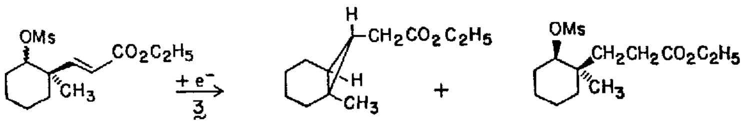
Table 2. Yields of Anticipated Cyclization Products Obtained from Cyclic α,β-Unsaturated Esters[5]

Substrate	Cyclization Product(s)	Yield(s)
 9		81%
 10		60%
	+	
		10%
 11	—	0%
 12		55%
 13	 14	98%[a]

(a) A 45:55 mixture of **13** and its epimer were reduced to give a 44% yield of **14**. Since the epimer does not cyclize, this constitutes a 98% yield of **14** from **13**.

unsaturated ester and the leaving group. As shown, simple cases such as **9** and **10** give synthetically useful yields of cyclization products (81% and 70%, respectively). The failure of **11** to provide any cyclization product illustrates an important mechanistic point. Sulfonate esters are known to undergo reductive cleavage of both the S-O bond [9] and the C-O bond.[10] Reductive C-O cleavage of the mesylate group of any of the substrates used in our study could, in principle, generate a carbanion, which could add to the α,β-unsaturated ester in a Michael addition to produce the observed products. If this were the mechanism, **10** and **11** should both yield the same carbanion and the same products. The failure of **11** to yield any cyclization products shows that it is the α,β-unsaturated ester which is reduced, and that the resulting anion radical does a classical backside S_N2 displacement of the mesylate anion. With the cis stereochemistry present in **11**, this type of displacement cannot readily occur and, as a result, no cyclization is observed.[11]

In the case of **13**, the reduction was carried out on a 45:55 mixture of **13** and its epimer **15** to give a 44% yield of **14** or a 98% yield based on **13**. When the reduction of the mixture of **13** and **15** was done in the presence of two equivalents of dimethyl malonate, a 41% yield of **14** and 47% yield of **16** was obtained. Since the anion radical generated from **15** cannot cyclize due to the requirements for S_N2 displacement, proton transfer occurs to this anion radical to produce **16**.



13 + 15 14 16

In summary, we have elucidated the scope, limitations and some of the mechanistic details of this synthetically useful reductive cyclization reaction.

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References and Footnotes

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4. For related cyclization reactions which are promoted by electrochemical reduction of α,β-unsaturated carbonyl compounds, see: (a) Nugent, S. T.; Baizer, M. M.; Little, R. D. *Tetrahedron Lett.* **1982**, *23*, 1339. (b) Scheffold, R.; Dike, M.; Dike, S.; Herold, T.; Walden, L. *J. Am. Chem. Soc.* **1980**, *102*, 3642. (c) Little, R. D.; Fox, D. P.; Hijfte, L. F.; Dannecker, R.; Sowell, G.; Wolin, R. L.; Moëns, L.; Baizer, M. M. *J. Org. Chem.* **1988**, *53*, 2287. (d) Fox, D. P.; Little, R. D.; Baizer, M. M. *J. Org. Chem.* **1985**, *50*, 2202.
5. Cathodic reduction was carried out in an H-cell equipped with a platinum wire gauze anode, a mercury pool cathode and a saturated calomel reference electrode (SCE). Electrolyzed solutions consisted of 0.5 mmol of substrate in 30 mL of 0.2 M tetra-n-butylammonium perchlorate in dimethylformamide.
6. Satisfactory elemental analyses and exact mass molecular weights were obtained on all new compounds. All compounds exhibited ^1H NMR, ^{13}C NMR, and IR spectra which were consistent with the assigned structures.
7. Knipe, A. C.; Stirling, C. J. M. *J. Chem. Soc., B* **1967**, 808. Relative rates of intramolecular nucleophilic displacement to form 3-, 4-, 5-, and 6-membered carbocyclic rings were found to be 1.0, 1.5×10^{-6}, 1.0×10^{-2}, and 8×10^{-6}, respectively.
8. The syntheses of the starting materials listed in Tables 1 and 2 will be described in a full paper on this subject.
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11. The effect of dimethyl malonate on the reduction as described for the substrates listed in Table 1 also requires initial reduction of the α,β-unsaturated ester moiety.

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