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Two-Step Electrochemical Annulation for the Assembly of Polycyclic Systems

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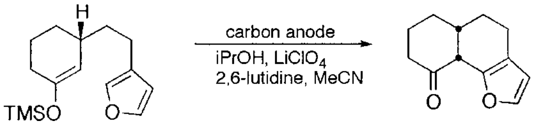
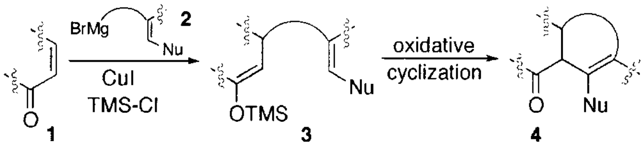
ABSTRACT



A two-step electrochemical annulation has been developed for the preparation of fused furans. The process involves an initial conjugate addition of a furyethyl cuprate and trapping of the enolate as the corresponding silyl enolether. The second step of the annulation involves the anodic coupling of the furan and the silyl enol ether to form a six-membered ring.

The construction of a carbocyclic framework, especially one with a quaternary center, is key to the rapid and efficient synthesis of many natural products.[1] We have developed a method for constructing functionalized ring systems through a two-step oxidative annulation process as illustrated in Scheme 1.

Scheme 1



This annulation strategy involves an initial conjugate addition of a fragment **2** containing a nucleophilic alkene to an α,β-unsaturated carbonyl derivative, trapping the resultant enolate to give **3**. The second step of the process, ring-closure, involves coupling of the two nucleophilic olefins triggered by oxidation[2] of one alkene to an electrophilic radical cation. In principle, either of the alkenes could undergo oxidation with the other serving as the nucleophilic terminator in the cyclization to produce **4**.

Furan was a particularly attractive system since Moeller and co-workers[3] had shown that furan could be oxidatively coupled to various nucleophiles using electrochemical oxidation. From a strategic perspective, the furan nucleus would offer the greatest synthetic flexibility since it can be easily converted to six- and seven-membered carbocycles through cycloadditions[4] or γ-lactones through oxidation.[5] To examine the proposed annulation,[6] we chose to form six-membered rings by electrochemical cyclizations (Scheme 2).

Conjugate addition of 3-furylethylmagnesium bromide **6** to cyclohexenone in the presence of trimethylsilyl chloride and TMEDA[7] led to the formation of the sensitive silyl

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[1] (a) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388. (b) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037.

[2] For other oxidative reactions of silylenol ethers see: (a) Snider, B. B.; Shi, B.; Quickley, C. A. *Tetrahedron* **2000**, *56*, 10127. (b) Ryter, K.; Livinghouse, T. *J. Am. Chem. Soc.* **1998**, *120*, 2658. (c) Snider, B. B.; Lin, H. *Synth. Commun.* **1998**, *28*, 1913. (d) Hintz, S.; Mattay, J.; van Eldik, R.; Wu W.-F. *Eur. J. Org. Chem.* **1998**, 1583. (e) Hintz, S.; Frohlich, R.; Mattay, J. *Tetrahedron Lett.* **1996**, *37*, 7349. (f) Paolobelli, A. B.; Ceccherelli, P.; Pizzo, F.; Ruzziconi, R. *J. Org. Chem.* **1995**, *60*, 4954.

[3] (a) Moeller, K. D.; New, D. G. *Tetrahedron Lett.* **1994**, *35*, 2857. (b) New, D. G.; Tesfai, Z.; Moeller, K. D. *J. Org. Chem.* **1996**, *61*, 1578. For an excellent review, see: Moeller, K. D. *Tetrahedron* **2000**, *56*, 9527.

[4] Reviews: (a) Rigby, J. H.; Pigge, F. C. In *Organic Reactions*; Paquette, L. A., Ed.; Wiley and Sons: New York, 1997; Vol. 51, p 351. (b) Kappe, C. O.; Murphree, S. S.; Padwa, A. *Tetrahedron* **1997**, *53*, 14179−14233.

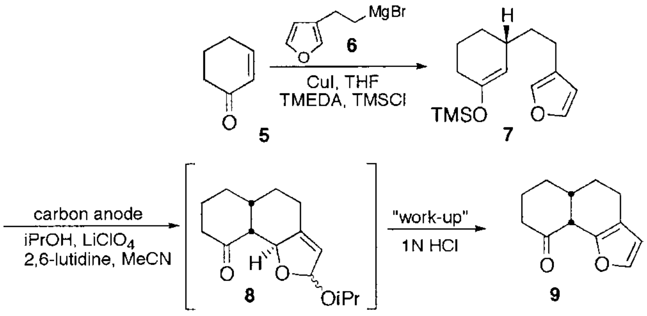
[5] Kuwajima, I.; Urabe, H. *Tetrahedron Lett.* **1981**, *22*, 5191.

[6] Synthesis of annulated furans: Padwa, A.; Murphree, S. S. *Org. Prep. Proc. Int.* **1991**, *23*, 545.

[7] (a) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6019. (b) Horiguchi, Y.; Matsuzawa, S.; Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1986**, *27*, 4025.

10.1021/ol026771k CCC: $22.00

Scheme 2



enolether **7** that was used without the benefit of further purification. Initial attempts to effect electrooxidative ring closure using methanol as a cation terminator were frustrated by competitive methanolysis of the silyl enolether. This unwanted reaction could be eliminated by the use of less reactive 2-propanol. Under these conditions, the annulated furan **9** was formed after a mildly acidic workup. Although initial electrolyses were conducted at a 0.4 M concentration of the electrolyte, it was determined that concentrations as low as 0.1 M provided successful cyclizations. The addition of 2,6-lutidine as an acid scavenger was also beneficial. Although additives were an important parameter, the nature of the electrode system was the most critical factor in the cyclization (Table 1).

Table 1. Electrode Optimization for the Synthesis of **9**

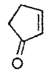
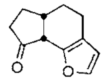
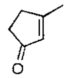
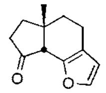
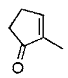
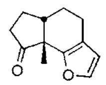
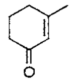
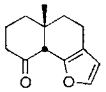
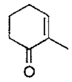
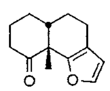
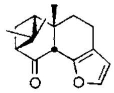
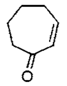
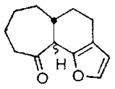
entry[a]	anode material	cathode material	current density[b] (mA/cm^2)	yield %[c]
1	carbon	steel	0.5	68
2	carbon	steel	1.0	66
3	carbon	steel	5.0	35[d]
4	carbon	steel	10.0	10[d]
5	carbon	carbon	0.5	67
6	platinum	carbon	0.5	27[d]
7	platinum	carbon	0.1	54
8	RVC	carbon	N/A	30[d]
9	RVC	carbon	N/A	35

[a] Reaction conditions: 0.02 M substrate, 0.4 M $LiClO_4$, 0.1 M lutidine in a 4:1 acetonitrile/2-propanol solution. All reactions were run under constant current conditions in an undivided cell. [b] Current density was approximated by dividing the applied current by the surface area of the electrode. [c] Yield is reported for two steps based on the starting enone. [d] The amount of charge consumed was 2−3 times the theoretical amount (2 F/mol).

Current density proved to be the most important characteristic of the electrode. This refers to the amount of current applied per unit area of electrode surface. As the current density increased for a given electrode (entries 1−4), the yield of the cyclized product dropped significantly and high molecular weight products were formed. Moreover, when the reaction was conducted at a high current density, the amount of charge consumed was many times greater than the theoretical 2 Faraday/mol. With sufficiently low current densities (0.5−1 mA/cm^2) the amount of charge required to completely consume the starting enolether was nearly the theoretical amount. Surprisingly, electrodes that have a high surface area and thus a low current density such as reticulated vitreous carbon[8] (RVC) were far inferior to typical graphite electrodes. High current densities may favor the formation of oligomers[9] by producing high concentrations of electroactive species at the electrode.

With an optimized method in place, a series of annulations were examined to establish the scope of the method (Table 2).

Table 2. Electrochemical Annulation Reactions

entry[a]	enone	product	yield[b]
10			64%
11			78%
12			64%
13			76%
14			65%
15			69%
16		 cis/trans : 1/4	58%

[a] Reaction conditions: 0.02 M substrate, 0.1 M $LiClO_4$, 0.04 M lutidine in a 4:1 acetonitrile/2-propanol solution. All reactions were run under constant current conditions in an undivided cell. [b] Yield is reported for two steps based on the enone.

The electrochemical annulation was highly effective with five- and six-membered enones delivering the corresponding indanones and decalones in very good yield (64−78% over two steps). The process was compatible with the creation of quaternary centers either at the cuprate addition step (e.g., **11)** or during the electrocyclization (e.g., **12**). Additionally, it was determined that these reactions were extremely stereoselective, delivering the cis-fused products exclusively. This high degree of stereocontrol eroded completely in the

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(8) Frey, D. A.; Wu, N.; Moeller, K. D. *Tetrahedron Lett.* **1996**, *37*, 8317.

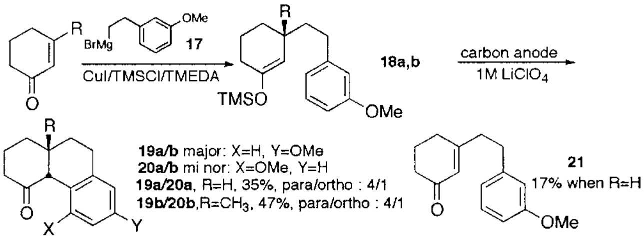
(9) For example, Kolbe dimerization is enhanced at high current densities: Coleman, J. P.; Lines, R.; Utley, J. H. P. *J. Chem. Soc., Perkin Trans. 2* **1973**, 1064.

closure onto a cycloheptyl system (entry 16) where the stereoselectivity reversed, giving the trans-fused system in a 4:1 predominance over the cis isomer. This change may reflect the increased flexibility of the seven-membered ring that allows alternative stereochemical paths to occur.

During the course of these studies we gained insight into the nature of the reaction through structural characterization of the initial reaction product. Although the furan **9** is the typical product isolated, the moderately unstable dihydrofuran **8** could be isolated if the acidic workup was eliminated. The structure of the intermediate, including relative stereochemistry, was determined by NMR and shown to exist as a 1:1 mixture of two isomeric acetals. The three contiguous centers at the ring junctions were formed in a single configuration indicating that the cyclization occurred in a cis fashion with the furan approaching the enolether through an exo orientation. The initial formation of a nonfuran intermediate may be important in that it protects the ring from over-oxidation.

We have also examined the ability of an electron-rich benzenoid ring to function as the cyclization terminator (Scheme 3).

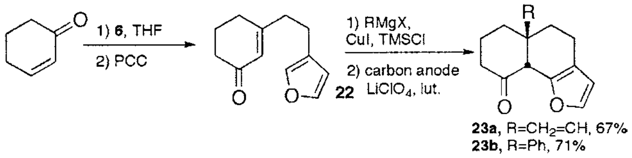
Scheme 3



To examine this closure, the Grignard reagent **17** was added in conjugate fashion to cyclohexenone to generate the corresponding enolether **18a** in high yield. Electrolysis of the silyl enolether under the conditions optimized previously failed to generate any ring-closed products and resulted primarily in the formation of polymeric materials. However, increasing the electrolyte concentration to 1 M resulted in a moderate yield of the ring-cyclized product as a 4:1 mixture of regioisomers. Interestingly, enone **21** was isolated as a significant byproduct. This compound probably arises by proton loss from the initially generated radical cation, suggesting that trapping of the radical cation by the anisyl group is somewhat slower than furan. This elimination product could be suppressed by employing 3-methylcyclohexenone in the annulation reaction. Electrochemical cyclization of **18b** was somewhat better, although still giving only a 47% yield. Although the arenes can function in the cyclization, it is clear that furan is far superior in this annulation process.

The flexibility of the annulation could be extended by reversing the order in which groups are added to the enone prior to the electrochemical cyclization (Scheme 4).

Scheme 4



1,2-Addition of the Grignard reagent **6** to cyclohexenone followed by oxidative rearrangement delivered the furyl-appended enone **22**. Addition of groups such as vinyl and phenyl was easily accomplished, and electrolysis of the resulting enolethers led to smooth cyclization to give decalins **23a** and **23b** in very good yield.

The development of this two-step annulation protocol provides direct access to polycyclic systems containing annulated furans. We are currently employing cyclization product **11** in combination with an oxyallyl cation cycloaddition to gain entry into the cyathane natural products.[10] Studies on the closure of different ring sizes and the use of other terminator groups will be reported in due course.

Acknowledgment. We are grateful to the National Science Foundation for support of this research.

Supporting Information Available: Experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL026771K

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(10) Wright, D. L.; Whitehead, C. R.; Sessions, E. H.; Ghiviriga, I.; Frey, D. A. *Org. Lett.* **1999**, *1*, 1535.