

# Electrochemical annulation of five-membered rings through dearomatization of furans and thiophenes†

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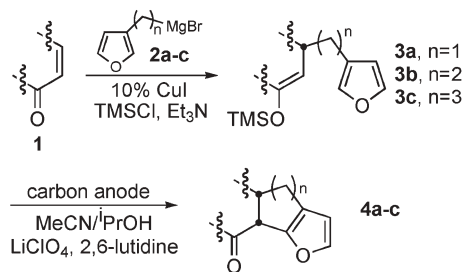
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A new methodology for the annulation of five-membered carbocyclic rings onto enones through the dearomatizing electrochemical cyclization of furans and thiophenes has been developed.

Over the past several years, we have been developing an electro-oxidative annulation strategy based on the coupling of silyl enoethers and furans to prepare a variety of carbocyclic systems (Scheme 1).

This two-step protocol involves the silyl-accelerated addition of furyl-appended cuprates **2a–c** to an enone, **1**, to give the silyl enoethers **3a–c**. Anodic oxidation<sup>1</sup> of **3** occurs at the silyl enoether<sup>2</sup> to produce a radical-cation intermediate, which is trapped in a furan-terminated cyclization to produce the annulated heterocycles **4a–c**. We have found that six-membered rings ( $n = 2$ ) can be formed easily by this route,<sup>3</sup> and we have recently extended this methodology to seven-membered ring systems<sup>4</sup> ( $n = 3$ ). The adaptation of this route to five-membered ring annulations was attractive as few general methods exist for this type of transformation.<sup>5</sup> However, all efforts to effect a five-membered annulation ( $n = 1$ ) through the route shown above have been frustrated, as the corresponding cuprate, **2a**, undergoes addition to the enone at both the  $\alpha$ -position and the 2-position of the furan to generate mixtures of silyl enoethers. Herein, we report an adaptation of this methodology to effect five-membered ring annulation that highlights how unique reaction manifolds can be accessed under electrochemical conditions.



**Scheme 1** General strategy for the synthesis of annulated furans (3  $\rightarrow$  2 closure).

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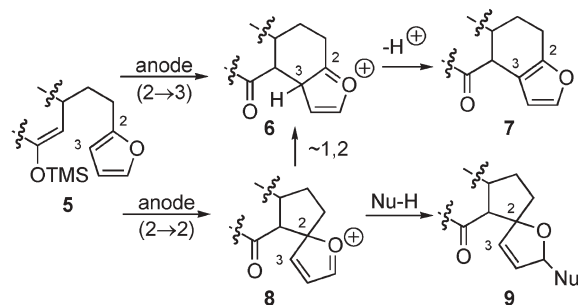
† Electronic Supplementary Information (ESI) available: Experimental procedures and characterization data for new compounds. See DOI: 10.1039/b513532j

Whereas the previous studies had focused on a (3  $\rightarrow$  2) closure of the furyl trap, the reverse situation, whereby the furan is tethered at the 2-position, presented the opportunity for a different mode of ring closure (Scheme 2).

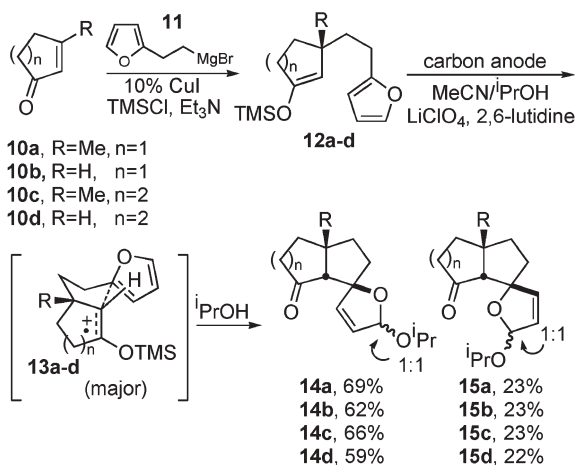
Electrolysis of a compound such as **5** could lead directly to an annulated furan, **7**, by attack at C3 to give oxocarbenium ion **6**. However, it is well known that furans are significantly more nucleophilic at C2, and kinetic closure to cation **8** could be followed by trapping with a nucleophile to give the addition product **9**, the result of a formal [3C + 2C] annulation. Literature precedence,<sup>6</sup> based on traditional, cationic cyclization conditions, suggested that **7** was the likely product of the reaction, either through direct attack at C3 or *via* a 1,2-shift of **8**. However, the conditions of electrolysis are quite unique and differ substantially from typical cationic conditions in that large quantities of good nucleophiles (isopropanol in this case) are tolerated in the reaction. This is the case since the cations are generated on an electrode surface rather than through a reactive Lewis or protic acid. If **8** is indeed formed kinetically, then it seemed possible to intercept the cation prior to rearrangement.<sup>7</sup>

To study this reaction we prepared the silyl enoethers **12a–d**, arising from the addition of furyl cuprate **11†** to enones **10a–d** (Scheme 3).

Electrolysis of silyl enoethers **12a–d** under the previously described conditions led to a  $\sim 3 : 1$  mixture of spirodihydrofuran acetals **14a–d** and **15a–d**, each as a mixture of anomers, assigned by NMR methods. No products arising from attack at C3 were observed. The major isomers apparently arise through an *endo* transition state **13a–d**. Despite the moderate level of diastereoselectivity with respect to the spiro carbon, the total conversion from **12a–d** was so high that overall isolated yields of 59–69% of the major isomer from **10** could be realized. These compounds could be taken on to highly functionalized building blocks, such as **16** and **17**, by hydrolysis and Fetizon's oxidation.<sup>8</sup> Lactone **16**,



**Scheme 2** Divergent reaction modes of a C2-tethered furan leading to five- or six-membered rings.

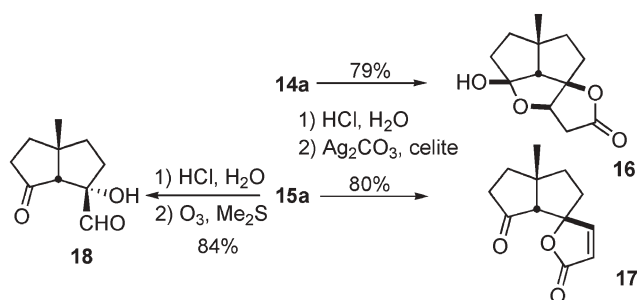


Scheme 3 An electrochemical [3C + 2C] annulation.

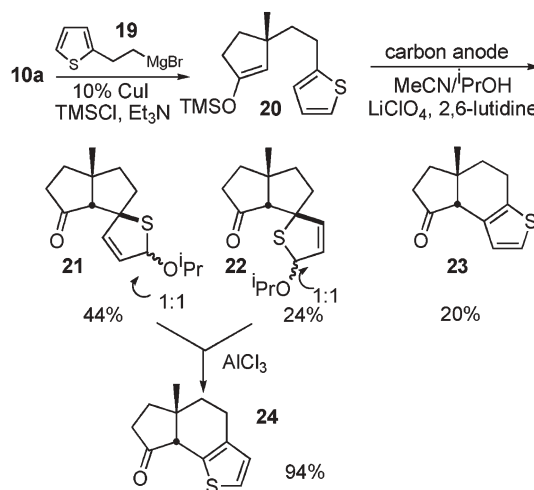
arising from the major isomer, is positioned to form a bridging hydrate **16**, while the minor isomer is isolated as the  $\alpha,\beta$ -unsaturated lactone **17**, thus verifying the earlier NMR assignments. The adduct could also be converted to the interesting  $\alpha$ -hydroxy aldehyde **18** by ozonolysis of the corresponding lactol (Scheme 4).

The ability to trap out the kinetically formed oxocarbenium ion prior to rearrangement may relate to the relatively modest resonance stabilization energy (RSE  $\sim 16$  kcal mol<sup>-1</sup>) endemic to furan, which is easily compensated-for by the formation of the C–O  $\sigma$  bond, a process Moeller *et al.*<sup>9</sup> and we<sup>2</sup> have observed in the electrolysis of various furans. We speculated that heterocycles with more resonance stabilization energy would prefer a substitution pathway and examined this by using a thiophene (RSE  $\sim 29$  kcal mol<sup>-1</sup>) terminator. Again, ample literature precedence indicated that the generation of electrophilic centers tethered to the 2-position of a thiophene leads exclusively to cyclization at the 3-position, although kinetic attack at C2 has been suggested.<sup>10</sup> Utilizing the 2-substituted thiophene cuprate derived from **19**† produced **20**. Surprisingly, electrolysis of this silyl enol ether led primarily to the formation of the five-membered annulation products **21/22** through dearomatization of the thiophene (Scheme 5).

The stereoselectivity at the spiro center was lower than the furan, although the *endo* mode predominated. In addition to these dihydrothiophene adducts, a small amount of the expected linear thiophene, **23**, was isolated as a single isomer. Interestingly, treatment of a mixture of **21/22** with a Lewis acid led to the



Scheme 4 Some transformations of the spiroannulated product.



Scheme 5 A thiophene based [3C + 2C] annulation.

exclusive production of annulated thiophene **24** in excellent yield. This reaction presumably regenerates the thiocarbenium ion intermediate, but under these typical cationic conditions, a rapid 1,2-migration of the methylene group ensues to produce **24**. The preference for methylene over methine migration is likely to be attributed to the electron-withdrawing nature of the adjacent ketone.<sup>11</sup> This reaction again illustrates that substantially different modes of reaction are available under electrochemical conditions that are not possible under more traditional methods of inducing cationic cyclizations. The exclusive formation of **24** also suggests that the thiophene **23**, observed in the original electrolysis, arises directly from capture at C3.

The synthetic application of electrochemical methods can make reaction modes available that are not possible using traditional chemical oxidants and reductants. In this report, we have shown how the normal manifold of aromatic substitution can be altered to provide a new method for the formation of five-membered carbocyclic systems through the dearomatization of furans and thiophenes.

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## Notes and references

† Bromides were prepared from the corresponding heteroaryl ethanol. See supporting information for details.†

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