Furan Synthesis via a 4 + 1 Ring-Building Strategy - An Approach to 1,3-Diacylfurans

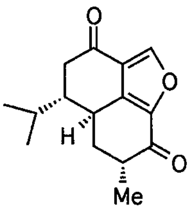
George A. Kraus* and Zhiwen Wan

Department of Chemistry, Iowa State University, Ames, IA 50011, USA

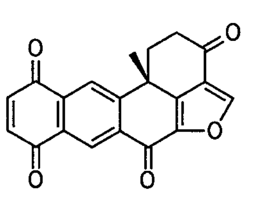
Received 14 April 1997

Abstract: The reaction of 2-acyl cycloalkenones with enolates affords 1,3-diacyl furans in good yields.

Many biologically active natural products containing the furan subunit have been discovered.[1] Although the majority of these compounds contain mono- and di-substituted furans, an increasing number of biologically active natural products, including hibiscone C (**1**),[2] and halenaquinone (**2**),[3] contain trisubstituted furans. As part of a program to better develop the synthetic utility of furans,[4] we needed a direct synthetic route to the highly functionalized furan units present in **1** and **2**.

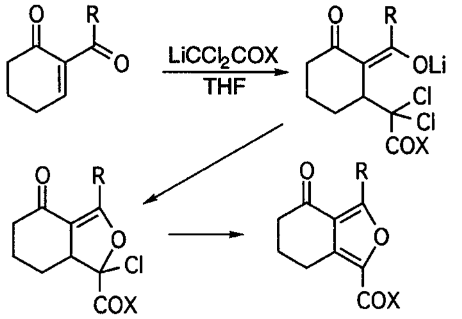


1



2

The key ring-forming reaction is illustrated below. It begins with a Michael addition reaction to an acyl cycloalkenone[5] under anhydrous conditions, in analogy with the pioneering work of Holton and coworkers.[6]

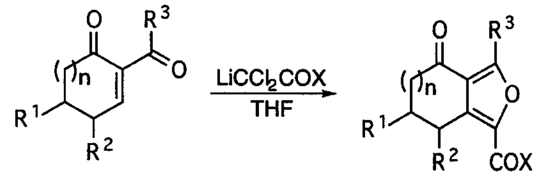


The resulting enolate displaces the chloride to afford an intermediate chloro ether which dehydrohalogenates to the furan. Datta and coworkers have reported a furan synthesis that is based on the reaction of bis-(methylthio)methylene cyclohexanone with the enolate of ethyl bromoacetate.[7] Harris has also reported a related furan synthesis based on the reaction of sulfonium ylides with unsaturated ketones.[7]

The scope and limitations of the reaction are depicted in Table 1. This reaction is applicable to enones contained in five-, six- and seven-membered rings. Michael donors can be dichloroesters or dichloroketones.[8] Michael acceptors can be keto aldehydes or diketones.[9] Dehydrohalogenation in entries 5 and 6 required diazabicycloundecene (DBU). In these cases, the chloroether intermediates could be isolated. The unusual stability of these two chloroethers is surprising, and may reflect a conformational effect related to the alkyl group on the cyclohexanone ring. The failure of the reaction in entry 7 may be attributable to steric hindrance.

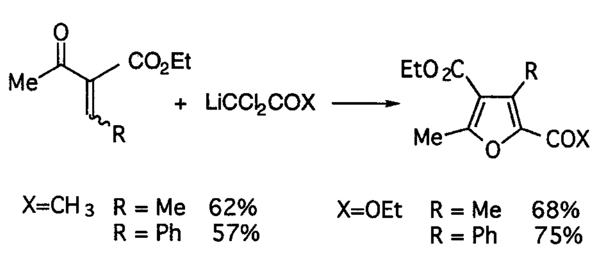
Acyclic keto esters also react well as illustrated below. In these cases no intermediate chloroethers were isolated. The yields in this one-step reaction compare well with those of comparable multistep routes to these systems.[10]

Table 1. Synthesis of Furans from Enediones

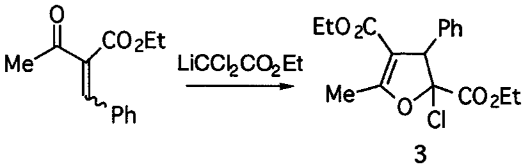


Entry	n	R_1	R_2	R_3	X	% yield
1	1	H	H	H	OEt	70
2	1	H	H	Me	OEt	86
3	0	H	H	H	OEt	50
4	2	H	H	H	OEt	52
5	1	iPr	H	H	OEt	63[a]
6	1	H	Me	H	OEt	30[a]
7	1	H	tBu	H	OEt	0
8	1	H	H	Me	Me	70
9	2	H	H	H	Me	55

a: The yield includes treatment of the chloroether with DBU in toluene



In order to better understand the course of this reaction, we reacted one equivalent of the lithium enolate of ethyl dichloroacetate with phenylmethylene ethyl acetoacetate at -78 °C and quenched the reaction at -78 °C with acetic acid. The product was dihydrofuran **3**. This compound could be converted into the furan using DBU.



3

The ready availability of the starting materials and the mild reaction conditions employed in the 4+1 cyclization reaction make this furan synthesis a useful complement to existing methodology. The product from entry 1 may be a useful intermediate for the synthesis of **1**.

Acknowledgement - We thank the ISU Center for Advanced Technology Development and the National Science Foundation for financial assistance.

References

1. Athanasin: Bojack, G.; Bornowski, H. *Tetrahedron,* **1993**, *49*, 6515. Isonakafuran-9: Fontana, A.; Avila, C.; Martinez, E.; Ortea, J.; Trivellone, E.; Cimino, G. *J. Chem. Ecol.*, **1993**, *19*, 339. For a review of furanosesquiterpene synthesis, see: Allen, A. J.; Vaillancourt, V.; Albizatti, K. F. *Org. Prep. Proc. Intl.*, **1994**, *26*, 1-84.
2. Thomson, R. H.; Ali, S.; King, T. J.; Ferreira, M. A. *J. Chem. Soc. Perkin Trans. I,* **1980**, *249*.
3. Roll, D. M.; Scheuer, P. J.; Matsumoto, G. K.; Clardy, J. *J. Am. Chem. Soc.,* **1983**, *105*, 6177.
4. Kraus, G. A.; Gottschalk, P. *Tetrahedron Lett.* **1983**, 2727.
5. Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Org. Chem.,* **1974**, *39*, 2133.
6. Holton, R. A.; Williams, A. D.; Kennedy, R. M. *J. Org. Chem.*, **1986**, *51*, 5480.
7. Datta, A.; Pooranchand, D.; Ila, H.; Junjappa, H. *Tetrahedron,* **1989**, *45*, 7631. Harris, C. M.; Cleary, J. J.; Harris, T. M. *J. Org. Chem.* **1974**, *39*, 72.
8. Dichloroacetophenone did not participate in this reaction.
9. To a solution of 10 mmol of LDA in THF at -78 °C was added dropwise a 1 M THF solution of ethyl dichloroacetate (10 mmol). The solution was stirred at -78 °C for 1 h. The Michael acceptor (5 mmol in 10 mL THF) was then added and the solution was stirred at -78 °C for 3 h and allowed to warm to rt. Ammonium chloride was added and the solution was partitioned between ether and water. The ether layer was dried and purified by sgc using hexanes: ethyl acetate.

   Diethyl 5-Methyl-3-phenylfuran 2,4-dicarboxylate. NMR ($CDCl_3$) δ 1.02 (t, J=7.5 Hz, 3H), 1.11 (t, J=7.5 Hz, 3H), 2.70 (s, 3H), 4.08 (q, J=7.5 Hz, 2H), 4.17 (q, J=7.5 Hz, 2H), 7.30 (m, 5H). CMR ($CDCl_3$) δ 13,7, 13.9, 14.6, 60.3, 60.8, 127.4, 127.8, 127.9, 129.5, 131.8, 134.6, 138.9, 158.7, 162.0, 163.2. MS m/z 302. mp 87-88 °C (cyclohexane), lit[10] mp 86-87 °C (cyclohexane).
10. Taylor, M. D.; Anderson, K. R.; Badger, E. W. *J. Heterocycl. Chem.,* **1989**, *26*, 353.