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Methylsulfenylation of Thioacetals as a Method for Synthesizing 2-Thio-Substituted Furans

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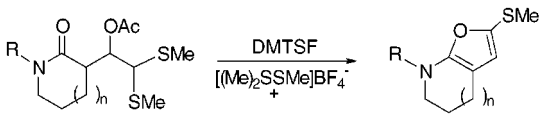
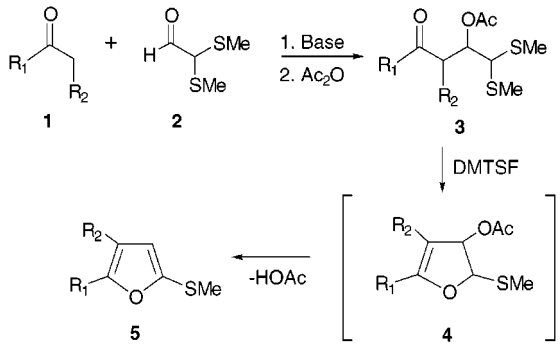
ABSTRACT



The dimethyl(methylthio)sulfonium tetrafluoroborate induced cyclization of various bis(methylsulfanyl) carbonyl compounds is described. The reaction proceeds by methylthiolation of the thioacetal group to give a thionium ion which undergoes subsequent cyclization with the neighboring carbonyl group. This is followed by an elimination reaction to furnish the furan ring.

Substituted furans have often been employed as sources of latent functionality for the synthesis of natural products.[1] Thio-substituted furans are particularly attractive intermediates that have found widespread usage in organic synthesis. They undergo a variety of reactions including addition/elimination,[2] nickel-catalyzed Grignard coupling,[3] Michael addition,[4] ortho-metalation,[5] acid hydrolysis to butenolides,[6] and [4 + 2]-cycloaddition chemistry.[7] Although a number of synthetic procedures are available for their formation,[5,8] most of the existing methods often require harsh conditions and are frequently based on the use of a preexisting furan ring. Examples include the addition/elimination of thiols,[9] sulfanylation of ortho-metalated anions,[10] metalation of disulfides,[5] and alkylation of furan thiolates.[11] Our own interest in this area stems from the facility with which 2-amino- and 2-thioalkyl-substituted furans undergo Diels−Alder cycloaddition chemistry and the potential use of the resulting oxabicyclic adducts for alkaloid synthesis.[12] In this Letter we describe a highly efficient synthesis of 2-alkylthio-substituted furans which is based on an aldol condensation of a carbonyl compound with bis(methylsulfanyl)acetaldehyde (**2**) followed by acetylation with Ac_2O (Scheme 1).

Scheme 1



Methylsulfenylation of one of the thiomethyl groups of the resulting acetate **3** with dimethyl(methylthio)sulfonium tetrafluoroborate (DMTSF)[13] induces a Pummerer cyclization to

(1) Lipshutz, B. H. *Chem. Rev.* **1986**, *86*, 795. Sargent, M. V.; Dean, F. M. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1984; Vol. 4, p 599. Frey, H. *Synlett* **1993**, 905.

(2) Kada, R.; Knoppova, V.; Kovac, J.; Vecera, Z. *Collect. Czech. Chem. Commun.* **1980**, *45*, 1831.

(3) Takei, H.; Miura, M.; Sugimura, H.; Okamura, H. *Chem. Lett.* **1979**, 1447.

(4) Kraus, G. A.; Gottschalk, P. *Tetrahedron Lett.* **1983**, *27*, 2727.

(5) Nolan, S. M.; Cohen, T. *J. Org. Chem.* **1981**, *46*, 2473.

(6) Okazaki, R.; Negishi, Y.; Inamoto, N. *J. Org. Chem.* **1984**, *49*, 3819.

(7) Eugster, C. H.; Balmer, M.; Prewo, R.; Bieri, J. H. *Helv. Chim. Acta* **1981**, *64*, 2636. Kotsuki, H.; Mori, Y.; Ohtsuka, T.; Nishizawa, H.; Ochi, M.; Matsuoka, K. *Heterocycles* **1987**, *26*, 2347. Harwood, L. M.; Ishikawa, T. J.; Phillips, H.; Watkin, D. *J. Chem. Soc., Chem. Commun.* **1991**, 527. Wu, H. J.; Yen, C. H.; Chuang, C. T. *J. Org. Chem.* **1998**, *63*, 5064.

(8) McDougal, P. G.; Oh, Y. I. *Tetrahedron Lett.* **1997**, *38*, 6869. Tsay, H. *Tetrahedron Lett.* **1997**, *38*, 6869.

(9) Dann, O.; Moeller, F. *Chem. Ber.* **1949**, *82*, 76.

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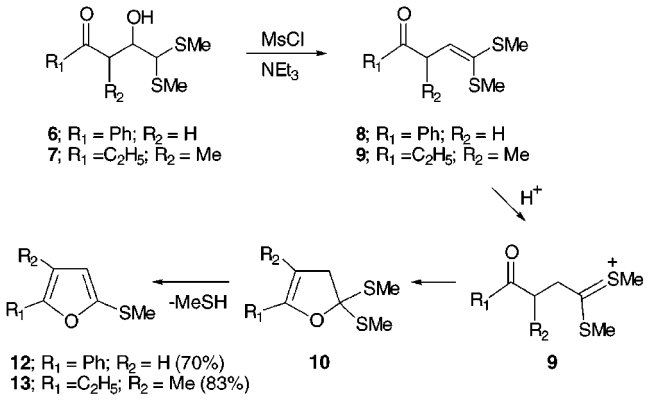
give dihydrofuran **4**. This is followed by elimination of acetic acid to furnish the desired furan **5** in excellent yield.

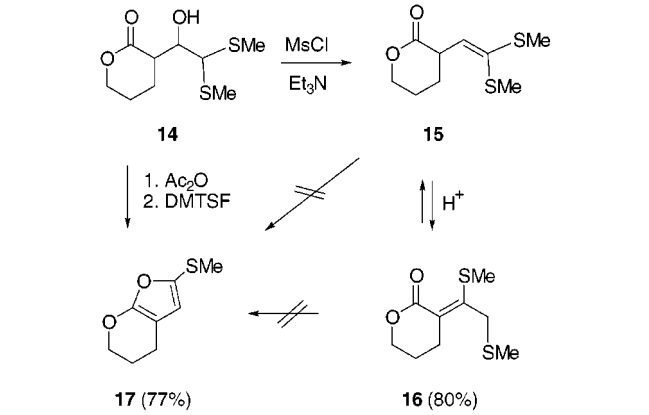
The above method was discovered in the course of an attempted synthesis of several 2-thiomethyl-5-alkoxy or 5-dialkylamino cyclic furans such as **17** or **24** (vide infra). In planning an approach to these compounds, we relied on earlier studies in our laboratory which showed that the acid-catalyzed reaction of β-oxo ketene thioacetals **8** and **9** gave furans **12** and **13** in 70% and 83% yields, respectively. This reaction most probably proceeds by a protonation/cyclization/elimination sequence as outlined in Scheme 2.

Scheme 2



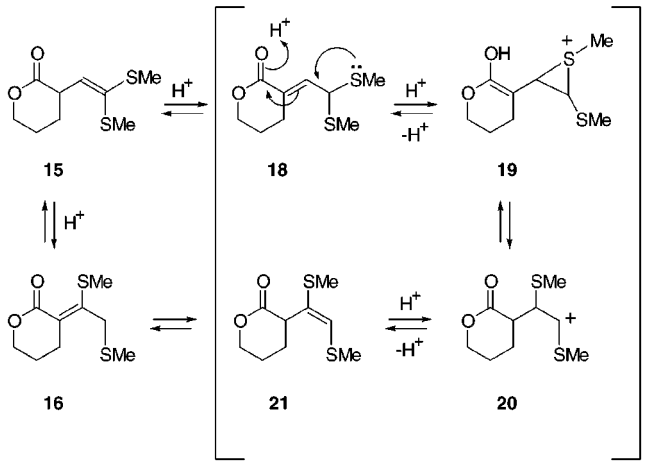
However, when this reaction sequence was applied to thioketene acetal **15**, prepared by dehydration of the aldol condensation product **14**, none of the desired furan **17** could be detected. Instead, the only product isolated (80%) corresponded to the rearranged thio-conjugated lactone **16**. Subjection of a sample of **16** to the acidic conditions gave thioketene acetal **15** (20%) in addition to recovered starting material (80%). This same equilibrium mixture (i.e., **15**:**16** = 1:4) was observed in the acid-catalyzed reaction of **15** (Scheme 3).

Scheme 3



The interconversion of **15** and **16** is believed to occur via the transient episulfonium ion **19** (Scheme 4). The critical

Scheme 4



step leading to the formation of **19** involves an initial 1,3-hydrogen shift of **15** to give **18** which is followed by conjugate addition of the neighboring thiomethyl group onto the activated π-bond. Once formed, episulfonium ion **19** can undergo a subsequent ring opening in the opposite direction to produce thionium ion **16** by deprotonation and double bond isomerization. A related set of reactions also takes place when **16** is subjected to the acidic conditions, eventually giving thioketene acetal **15** as the minor product (20%) from the equilibrating mixture.

The series of steps shown in Scheme 4, although credible in retrospect, was totally unexpected. Our inability to prepare furan **17** from the acid-catalyzed reaction of thioketene acetal **15** led us to consider some alternate ways to synthesize this compound.[14] It was known from earlier work in the literature that treatment of thioketals with DMTSF causes the carbon−sulfur bond to become labile upon methylthiolation.[15] The initially formed alkylthiosulfonium ion easily dissociates to produce a thionium ion and methyl sulfide. We reasoned that by converting the hydroxyl group present in lactone **14** into the corresponding acetate, it should be possible to promote cyclization of the lactone carbonyl group onto the resulting thionium ion formed from the DMTSF-induced reaction. Once the dihydrofuran ring has been forged, elimination of acetic acid should proceed readily to furnish

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(11) Annunziata, R.; Cinquini, M.; Cozzi, F.; Raimondi, L. *Tetrahedron Lett.* **1989**, *30*, 5013.

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(13) Trost, B. M.; Murayama, E. *J. Am. Chem. Soc.* **1981**, *103*, 6529. Trost, B. M.; Sato, T. *J. Am. Chem. Soc.* **1985**, *107*, 719. Commercially available from Aldrich Chemical Co.

(14) The difference in the acid-catalyzed behavior of **14** from that encountered with ketene thioacetals **8** and **9** may possibly be related to the lower concentration of the enol tautomer of the lactone, thereby permitting thiomethyl group migration to compete with cyclization. Further studies with other lactones are currently underway to help clarify this issue.

(15) Rice, J. L.; Favstritsky, N. A. *J. Am. Chem. Soc.* **1969**, *91*, 1751. Smallcombe, S. H.; Caserio, M. C. *J. Am. Chem. Soc.* **1971**, *93*, 5826. Kim, J. K.; Pau, J. K.; Caserio, M. C. *J. Org. Chem.* **1979**, *44*, 1544.

Scheme 5

22; R = Ts; n = 1
23; R = *t*-BuCO; n = 2

24; R = Ts; n = 1 (98%)
25; R = *t*-BuCO; n = 2 (78%)

the 2-thio-5-alkoxy-substituted furan **17**. Indeed, this two-step protocol worked extremely well and led to the formation of **17** in 77% overall yield.

The facility of this reaction sequence prompted us to investigate its use with several cyclic lactams. We found that this protocol could be successfully utilized with *N*-substituted lactams **22** and **23**, giving rise to the corresponding cyclic aminofurans **24** and **25** in 98% and 78% yields, respectively (Scheme 5).

In conclusion, we have described a mild method for the preparation of differentially substituted 2-thiomethyl furans from readily available starting materials. This method should be useful for the preparation of a wide assortment of thio-substituted furans containing acid sensitive functional groups. We are presently exploring the synthetic use of these furans in [4 + 2]-cycloaddition chemistry and will report our findings at a later date.

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Supporting Information Available: Text giving experimental procedures and characterization data for the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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