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LETTERS

A Useful Modification of the Garst-Spencer Furan Annulation: An Improved Synthesis of 3,4-Substituted Furans

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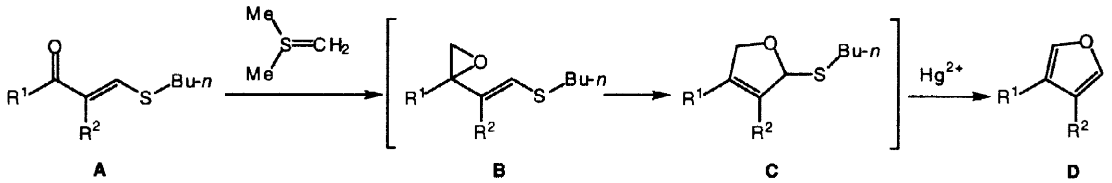
Abstract: The reaction of keto thioenol ether **6** with dimethylsulfonium methylide gives the isolable epoxide **7**, which smoothly rearranges under thermal conditions to yield the five-membered thioacetal **8**. Subsequent desulfurization/aromatization with a catalytic amount of iodine furnishes the desired furan **5** in greater than 70% overall yield.

The Garst-Spencer furan annulation[1] involves the epoxidation of a keto thioenol ether **A** with dimethylsulfonium methylide, rearrangement of the resultant epoxide **B** to a dihydrofuran **C**, and then desulfurization/aromatization with mercury salts to yield a 3,4-substituted furan **D** (Scheme 1). This annulation has been used successfully in various furan syntheses, including euryfurans[2] and furanoditerpenes.[3]

Scheme 1



In connection with the total synthesis of a steroidal alkaloid batrachotoxin (**1**),[4] we desired the furan-fused *cis*-decalins **4** and **5**, and the Garst-Spencer furan annulation appeared to meet our needs. However, application of the original Garst-Spencer protocol [$Me_3S^+BF_4^-$ (5 equivalents) / *n*-BuLi / DME, followed by $HgSO_4$ treatment] to the thioenol ether **2** gave disappointingly low yields. Tochtermann's modification, using the sulfur ylide generated from $Me_3S^+I^-$ and dimsyl sodium in DMSO-THF, has been reported to improve the overall yield considerably for many cases.[5] Indeed, under Tochtermann's conditions, the desired furan **3** was obtained in 70% overall yield from **2**, along with 20% of the recovered starting material.[6] Unfortunately, one problem concerning practicality was encountered when using this protocol: a large excess of the ylide (>5 equivalents) was required to consume **2** completely.[7] Eventually, this problem was overcome by employing new reaction conditions (3 equivalents of dimethylsulfonium ylide, generated from $Me_3S^+I^-$ with NaHMDS in THF, followed by $HgCl_2$ treatment). Under these modified conditions, **2** was converted to the desired furan **3** in 78% overall yield. In a sharp contrast, furan formation from **3** was accompanied by several by-products,

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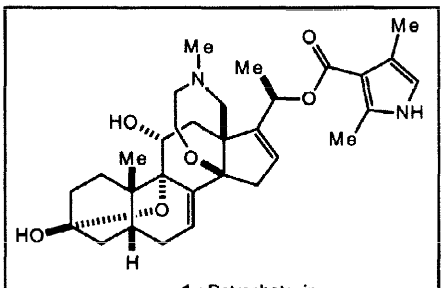
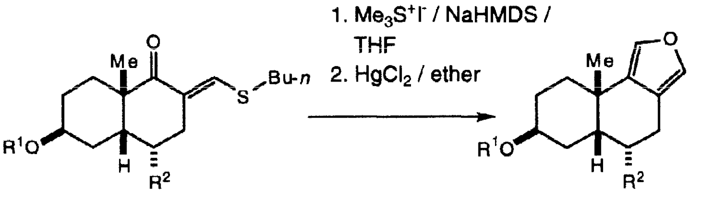
and the desired furan **5** was isolated in only 20% overall yield. Thus, efforts to improve the overall efficiency of the Garst-Spencer furan annulation were undertaken, with the specific goals being: (1) to eliminate or suppress the formation of all by-products[8] and (2) to enhance the ketone reactivity, possibly through substrate modification, in order to circumvent the need for a large excess of the ylide.



1 : Batrachotoxin

Scheme 2



2 : R^1=TBDPS, R^2=H
3 : R^1=TBS, R^2=OTBS

4 : R^1=TBDPS, R^2=H; 78% yield
5 : R^1=TBS, R^2=OTBS; 20% yield

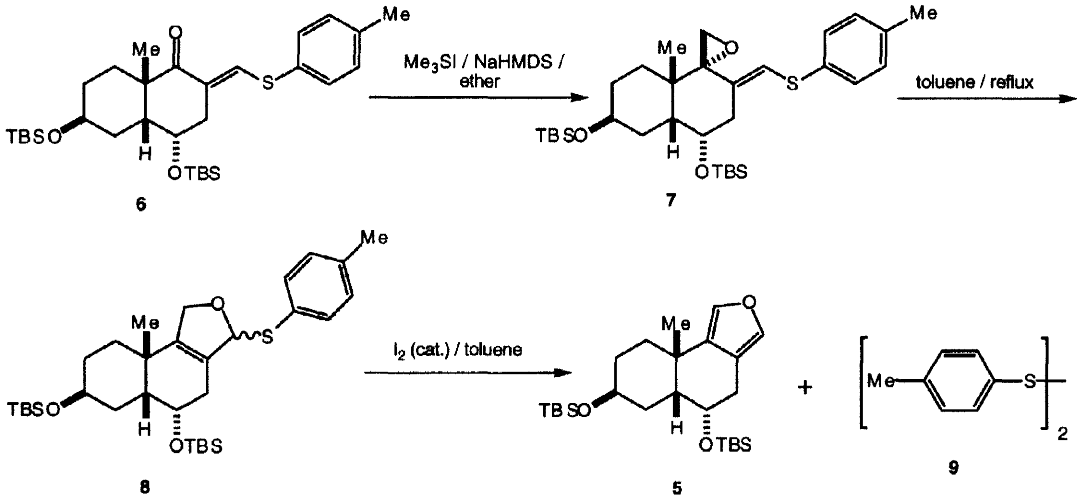
During optimization efforts in the **3**→**5** series, an important observation was made that guided us to the current solution. When the ylide reaction was conducted in a less polar solvent such as Et_2O, the overall yield was dramatically improved, up to 40~55%.[9] These results suggested that intermediate **B** in the Garst-Spencer furan annulation (Scheme 1) may undergo decomposition via an ionic mechanism in the reaction medium, leading to the formation of various by-products.[10] Consequently, it was thought that stabilizing intermediate **B** may improve the overall efficiency of this process. Along this line of analysis, we recognized the possibility that the electronegativity of the sulfur atom of the thioenol ether group might affect not only the stability of **B**, but also the reactivity of the ketone. Thus, the butylthio moiety of **3** was replaced with a thiocresol group[11] in expectation that the sulfur atom would be less electronegative due to delocalization of the sulfur lone pairs over the aromatic ring.

The cresolthioenol ether **6**[12] was synthesized from the corresponding ketone in 88% overall yield in two steps: (1) HCO_2Et (5 eq.) / NaH (2 eq.) / THF / RT and (2) thiocresol (4 eq.) / *p*-TsOH (0.1 eq.) / benzene / reflux (Dean-Stark trap). The carbonyl absorption in IR spectrum (neat) was observed at 1678 cm^{-1} for **6** and at 1674 cm^{-1} for **3**, which seemed to support our expectation. However, the chemical shifts in ^{13}C NMR spectrum did not show significantly large differences between **6** and **3**.[13]

The reaction of **6** with dimethylsulfonium methylide, generated from $Me_3S^+I^-$ (3 equivalents) and NaHMDS in ether, yielded the epoxy thioenol ether **7**[14] cleanly with an excellent mass recovery (Scheme 3). Interestingly, the epoxide **7** was stable to isolation, and ^1H NMR analysis revealed the crude product to be virtually pure and consisting of a single stereoisomer.[15] It is worth noting that the epoxide **7** was stable to aqueous work-up but rearranged to the dihydrofuran **8** during purification using silica gel or alumina chromatography. However, the rearrangement under these conditions was accompanied by the formation of several by-products. It was found that conversion of the epoxide **7** to the dihydrofuran **8** was best achieved in refluxing toluene, to yield a 1 : 1 mixture of the two diastereomers. Finally, desulfurization/aromatization of **8**, using a catalytic amount of iodine, furnished the desired furan **5**[16] in greater than 70% overall yield from **6**, along with tolyldisulfide (**9**).

In conclusion, it has been demonstrated that the stability of the epoxide intermediate in the Garst-Spencer furan annulation is significantly enhanced by a butylthio-to-cresolthio replacement, thereby allowing a cleaner and more efficient annulation. However, as both **3** and **6** were completely consumed under the reaction conditions, it is not obvious whether the replacement significantly alters the electrophilicity of the ketone. From a practical point of view, the current modifications add several appealing aspects to Garst-Spencer furan annulation, including improved overall efficiency and elimination of the use of mercury salts.

Scheme 3



Experimental procedures for Scheme 3: To a stirred suspension of $Me_3S^+I^-$ (10.1 g, 48.3 mmol, 3 equivalents) in Et_2O (1.0 L) at -10 °C was added a solution of NaHMDS (24.2 mL, 3 equivalents, 2 M in THF). The suspension was stirred for 1 h and cooled to -78 °C. To the mixture was then added a solution of thioenol ether **6** (9.00 g, 16.1 mmol) in ether. After 6 h at -60 °C, the reaction mixture was allowed to warm to 0 °C, diluted with hexanes, and quenched with water. The aqueous layer was extracted with hexanes (three times). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude epoxy thioenol ether **7** was dissolved in toluene (400 mL) and heated at 90 °C for 2 h, and the reaction mixture was cooled to rt. To the reaction mixture was added a toluene solution of I_2 (406 mg, 0.1 equivalent). After 15 min, the reaction mixture was concentrated *in vacuo*. Purification of the residue by silica gel chromatography (hexanes to 2% Et_2O-hexanes) afforded furan **5**[16] (5.10 g, 70%) as a white solid.

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References and Notes

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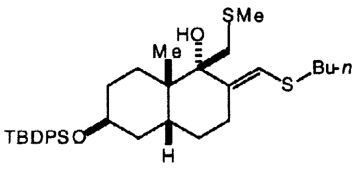
6. The Tochtermann's modification on **3** was first carried out by Dr. Timothy J. Grinsteiner in this laboratory.

7. Ketone **2** was completely consumed on small scale (0.2 mmol), but on larger scale complete conversion was never observed.

8. One of the by-products isolated, and characterized, from the reaction of **2** was **10**. The corresponding by-products were formed in the other series as well, although the amount of the by-products depended on the substrates and reaction conditions used.



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9. This procedure had been used for the total synthesis of racemic batrachotoxinin A quoted in Reference 4.

10. These observations indicated the epoxide derived from **3** to be significantly less stable than the epoxide derived from **2**, perhaps primarily for the steric reasons.

11. Thiophenol should have similar effects on the carbonyl group. However, because of its more unpleasant odor, we opted to use thiocresol over thiophenol.

12. ^{1}H-NMR (500 MHz, $CDCl_3$) of **6**: 7.68 ppm (1H, d, J = 1.5 Hz), 7.34 (2H, d, J = 8.1 Hz), 7.16 (2H, d, J = 8.1 Hz), 4.53 (1H, m), 4.09 (1H, br s), 2.79 (1H, dd, J = 16.8, 6.6 Hz), 2.39 (1H, dd, J = 10.6, 3.0 Hz), 2.35 (3H, s), 2.26 (1H, td, J = 13.1, 3.7 Hz), 2.02 (2H, m), 1.55-1.12 (4H, m), 1.14 (3H, s), 0.92 (9H, s), 0.89 (9H, s), 0.12 (3H, s), 0.11 (3H, s), 0.03 (6H, s). ^{13}C-NMR (125 MHz, $CDCl_3$) 199.8. ppm, 142.3, 138.3, 130.9, 130.1, 128.4, 66.1, 64.9, 47.6, 42.7, 33.7, 30.7, 29.6, 29.3, 26.9, 25.9, 21.1, 18.0, 18.1, -4.7, -4.9, -5.0. IR ($CHCl_3$) 2969 cm^{-1}, 2933, 2956, 1678, 1548. HRMS (FAB, NaI): $C_{31}H_{52}Si_2SO_3$ (M+Na$^+$) calcd. 583.3079, found 583.3099. A NOESY experiment established the stereochemistry of the thioenol ether.

13. The resonances of the α, β, and γ carbons of the thioenol ether moiety were observed at 199.8 ppm, 128.3, and 142.3 for **6** and at 199.6 ppm, 127.9, and 143.4 for **3**, respectively.

14. ^{1}H-NMR (500 MHz, $CDCl_3$) of **7**: 7.26 ppm (2H, d, J = 8.0 Hz), 7.12 (2H, d, J = 8.0 Hz), 6.13 (1H, d, J = 1.3 Hz), 4.15 (2H, m), 2.90 (1H, J = 4.1 Hz), 2.82 (1H, d, J = 4.1 Hz), 2.77 (1H, dd, J = 13.1, 4.5 Hz), 2.44 (1H, td, J = 13.1, 1.3 Hz), 2.32 (3H, s), 2.2-1.1 (7H, m), 1.05 (3H, s), 0.92 (9H, s), 0.89 (9H, s), 0.11 (3H, s), 0.88 (3H, s), 0.03 (6H, s).

15. The stereochemistry of **7** was concluded from a NOESY experiment in C_6D_6. The *cis*-decalin system of **2** adopted the conformation with the CH_2 group of the epoxide being equatorial. Distinct cross-peaks were observed between one of the epoxy methylene protons and the methyl protons as well as with 1α-H and 2α-H.

16. Data for **5**: ^{1}H-NMR (500 MHz, $CDCl_3$) 7.14 ppm (2H, s), 7.11 (1H, s), 4.39 (1H, m), 4.00 (1H, br s), 2.75 (1H, dd, J = 15.9, 6.6 Hz), 2.37 (1H, J = 15.9, 9.9 Hz), 1.96 (1H, m), 1.92 (1H, m), 1.83 (1H, m), 1.61 (1H, m), 1.59 (2H, m), 1.21 (3H, s), 1.07 (1H, t-like), 0.91 (18 H,m), 0.08 (6H, s), 0.03 (6H, s), 0.10 (3H, s), 0.03 (6H, s). ^{13}C-NMR (125 MHz, $CDCl_3$) 137.6 ppm, 136.9, 129.7, 128.2, 120.2, 67.2, 66.3, 57.4, 47.4, 42.4, 37.5, 33.4, 32.4, 29.9 28.0, 25.9, 25.6, 18.1. IR ($CHCl_3$) 2963 cm^{-1}, 2933, 2860, 1477, 1465, 1264. HRMS (CI): $C_{25}H_{46}Si_2O_3$ (M+NH$_4^+$) calcd. 468.3229, found 468.3313.