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LETTERS

# Intramolecular 4+3 Cycloadditions. Allylic Sulfones as Precursors to Vinylthionium Ions

Michael Harmata* and Mehmet Kahraman

*Department of Chemistry, University of Missouri-Columbia, Columbia, MO 65211*

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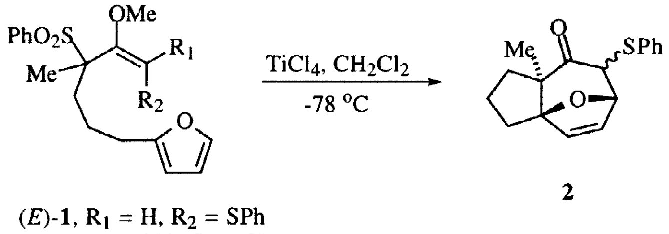
**Summary:** Treatment of a THF solution of (*E*)-**3** with n-BuLi followed by quenching with an electrophile generally results in regioselective alkylation alpha to the sulfone with the alkene possessing (*E*) stereochemistry in the major product. High selectivity for the (*E*) alkylation product can be achieved in the presence of small amounts of HMPA. When those (*E*) alkylation products possessing a diene moiety in the side chain are treated with Lewis acids, 4+3 cycloaddition products are formed in good to excellent yields. © 1998 Elsevier Science Ltd. All rights reserved.

Some time ago we reported that treatment of the allylic sulfone **1** with titanium tetrachloride resulted in the formation of cycloadduct **2** in good yield (67%) for only one of the two olefinic stereoisomers of **1**.[1] The compound which cyclized successfully was tentatively assigned the (*Z*) stereochemistry based on the fact that it was the more polar of the two isomers (TLC) of **1** and the resonance for the olefinic hydrogen was upfield (5.53 ppm vs. 5.65 ppm) of that of the other isomer. It was anticipated that the deshielding effect of oxygen would produce this result.[2] Both criteria, while not necessarily rigorous, pointed in the same direction and the assignment was made accordingly. This assignment is not correct.

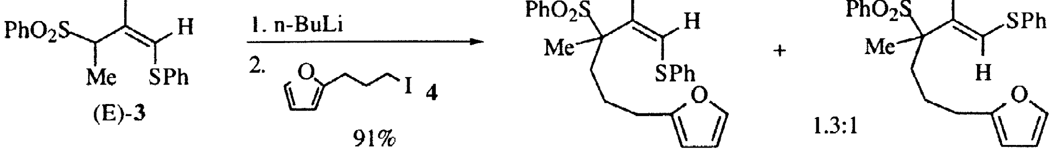


(*E*)-**1**, R$_1$ = H, R$_2$ = SPh
(*Z*)-**1**, R$_1$ = SPh, R$_2$ = H

**2**

**Equation 1**

Development of this methodology was not pursued with vigor, in part due to other progress in a related area.[3] However, recent renewed interest in the synthesis of the natural product widdrol prompted a more careful examination of the alkylation of (E)-**3**, particularly with respect to the isomeric distribution of the products.



(*E*)-**1**

(*Z*)-**1**

**Equation 2**

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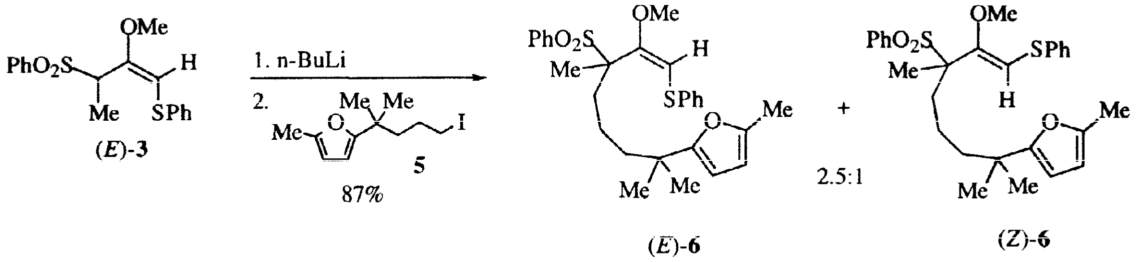
We had reported that treatment of a THF solution of (*E*)-**3** with n-BuLi at -78 °C and quenching of the resultant anion with 2-(3-iodopropyl)furan **4** followed by slow warming resulted in the formation of an approximately 1.3:1 mixture of two alkylation products in 91% yield.[1,4] Only the stereochemical assignment was wrong and the correct result is shown in equation 2.



**Equation 3**

This reassignment was made on the basis of the following experiment. Alkylation of the anion of (E)-**3** with iodide **5** gave a 2.5:1 mixture of products **6** in 87% yield (equation 3). As part of the characterization process, NOESY studies were performed. For example, for (*E*)-**6**, a cross peak was observed between the olefinic hydrogen and the methoxy group and between the allylic methyl and thiophenyl groups. On the other hand, for (*Z*)-**6**, weak cross peaks were observed between the olefinic hydrogen and the allylic methyl group and between the methoxy and thiophenyl groups.

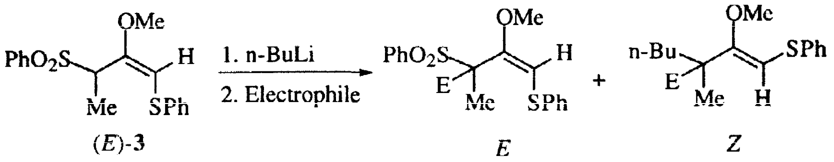


**Table 1. Lithiation and Trapping of (*E*)-3.**

| Entry | Conditions[a] | Electrophile | Product | *E*/*Z* Ratio[b] | Yield (%)[c,d] |
|---|---|---|---|---|---|
| 1 | A | $H_2O$ | **3** | 2.5:1 | – |
| 2 | B | $H_2O$ | **3** | 1:2.4 | – |
| 3 | C | $PhCH_2Br$ | **7** | only E | 84 |
| 4 | A | $PhCH_2Br$ | **7** | 19:1 | 64 |
| 5 | B | $PhCH_2Br$ | **7** | 1:7.5 | 52(57) |
| 6 | D | $PhCH_2Br$ | **7** | 1:8.3 | 30(44) |
| 7 | E | $PhCH_2Br$ | **7** | only E | 81 |

[a] Conditions: A: nBuLi, THF, -78 °C to rt for 5 min; recool to -78 °C; add electrophile after 5 min; slowly warm to rt. B: nBuLi, THF, -78 °C; to rt for 5 min; recool to 0 °C; add electrophile. C: n-BuLi, THF, -78 °C; add electrophile at -78 °C, slowly warm to rt. D: n-BuLi, THF, -78 °C to rt for 5 min; add electrophile. E: n-BuLi, THF/HMPA, -78 °C; add electrophile. All temperatures are bath temperatures. [b] Ratios were determined by NMR analysis of crude reaction mixtures. [c] Yields are after chromatographic purification. [d] Yields in paretheses based on recovered starting material.

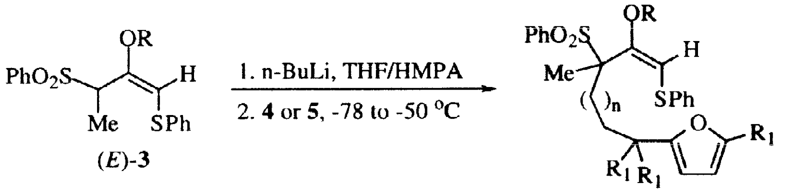
This result prompted a more thorough investigation of the behavior of the anion of (*E*)-**3**. Several other trapping experiments were conducted. The results are summarized in Table 1. Entries 1 and 2 show a temperature effect associated with the stereochemical outcome of the trapping event.[5] This effect is more dramatic when benzyl bromide was used as the electrophile. High stereoselectivity for either the *E* or *Z* isomer of **7** was possible depending on the temperature at which quenching took place.

The exact interpretation of the above results awaits further experimentation. Nevertheless, the data suggested that if alkylation could be performed at low temperature, the *E* stereoisomers of the alkylation products would result. We thus carried out alkylations in the presence of small amounts of HMPA using electrophiles which would ultimately produce precursors for 4+3 cycloaddition studies (Table 1, entry 7). The results are summarized in equation 4. Thus, treatment of a 0.2 M solution of (*E*)-**3** or (*E*)-**8** in 20% HMPA in THF at -78 °C with n-BuLi (1.1 eq. 2.4 M in hexanes) gave a solution of the anion. Addition of iodide **4** or **5** and warming to approximately -50 °C (bath temperature) resulted in alkylation and the regioselective formation of only the *E* isomers of the corresponding alkylation products in very good yields.

**Table 2. Chemical Shifts of Olefinic Protons.**[a]

| Entry | Compound | δ, E Isomer | δ, Z Isomer |
|---|---|---|---|
| 1 | **1** | 5.53 | 5.65 |
| 2 | **3** | 5.35 | 5.51 |
| 3 | **6** | 5.49 | 5.64 |
| 4 | **7** | 5.47 | 5.62 |
| 5 | **8** | 5.33 | – |
| 6 | **9** | 5.46 | – |

[a] In $CDCl_3$, downfield from TMS.



(*E*)-**3**

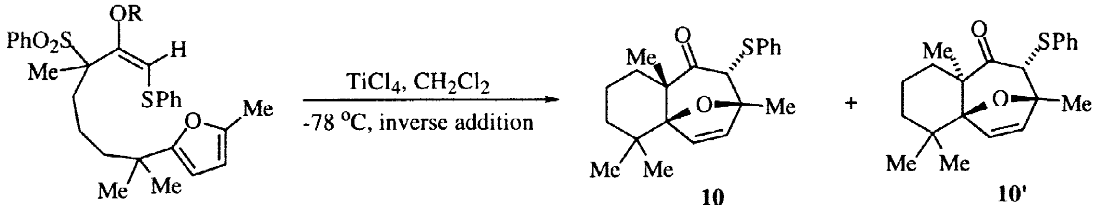
(*E*)-**3**, R = Me
(*E*)-**8**, R = Et

(*E*)-**1**, R = Me, $R_1$ =H, n =1; 80%
(*E*)-**6**, R = Me, $R_1$ =Me, n =2; 83%
(*E*)-**9**, R = Et, $R_1$ =Me, n =2; 76%

**Equation 4**

Stereochemical assignments in these studies were based on NOESY spectra for (*E*)- and (*Z*)-**6**. Sulfone (*E*)-**3** had been previously characterized by X-ray analysis.[1] In the course of this work, an X-ray structure for (*E*)-**7** was determined. These data were used in conjunction with chemical shifts of the olefinic hydrogens to assign stereochemistry to the remaining sulfones. Table 2 summarizes the data and demonstrates that the chemical shift of the olefinic protons for the (Z) isomers of the compounds studied consistently appears downfield of that of the corresponding (*E*) isomers. It is also worth noting that the (*Z*) isomers of the compounds in Table 2 are consistently less polar (TLC) than their (*E*) isomers.

In order to confirm that these compounds were useful for 4+3 cycloadditions they were treated with $TiCl_4$ under conditions of inverse addition. Substrate (*E*)-**1** cyclized in accord with our previous report to give the



(*E*)-**6**, R = Me
(*E*)-**9**, R =Et

**10**:**10'**, 1.1:1; 86%, from (*E*)-**6**
**10**:**10'**, 1:1; 72%, from (*E*)-**9**

**Equation 5**

corresponding 4+3 cycloadduct in 62% yield.[1] Sulfones (*E*)-**6** and (*E*)-**9** gave good to excellent yields of the 4+3 cycloaddition products, **10** and **10'** as an approximately 1:1 mixture of stereoisomers as shown in equation 5. The structures of **10** and **10'** were established by X-ray analysis of the corresponding sulfones.[6] Further details will be reported elsewhere.

In summary, we have shown that our initial, tentative assignments of stereochemistry of (*E*)-**1** and (*Z*)-**1** were incorrect. We have shown that the stereochemistry of the alkylation of the anion of **3** is dependent on reaction conditions and have developed a preliminary set of conditions which can produce E alkylation products with high selectivity and in good yield. This suggests that this methodology does have a future in 4+3 cycloaddition chemistry[7] and other areas in which carbon-carbon bond formation with vinylthionium ions may be significant.[8] Further studies of the alkylation of (*E*)-**3** and the conversion of **10** to widdrol are in progress. Results will be reported in due course.[9]

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## Reference and Notes

1. Harmata, M.; Fletcher, V. R.; Claassen II, R. J. *J. Am. Chem. Soc.* **1991**, *113*, 9861.
2. Hatada, K.; Takeshita, M.; Yuki, H. *Tetrahedron Lett.* **1968**, 4621.
3. Harmata, M., Jones, D.E. *Tetrahedron Lett.* **1996**, *37*, 783.
4. This information appears in the supplementary material for reference 1.
5. (Z)-**3** was not isolated and characterized. The fact that both isomers of **3** as well as all of the alkylation products had olefinic protons suggest that protonation and alkylation must have occurred alpha to the phenylsulfonyl group.
6. Harmata, M.; Kahraman, M.; Adenu, G. Unpublished results from these laboratories.
7. For a review of intramolecular 4+3 cycloadditions, see: (a) Harmata, M. *Tetrahedron* **1997**, *53*, 6235. (b) Harmata, M. In *Advances in Cycloaddition;* Lautens, M., Ed.; JAI: Greenwich, 1997, Vol. 4, pp 41-86.
8. For some examples of the use of vinylthionium ions in synthesis, see: (a) Hunter, R.; Simon, C. D. *Tetrahedron Lett.* **1986**, *27*, 1385. (b) Hunter, R.; Simon, C. D. *Tetrahedron Lett.* **1988**, *29*, 2257. (c) Hunter, R.; Carlton, L.; Cirillo, P. F.; Michael, J. P.; Simon, C. D.; Walter, D. S. *J. Chem. Soc. Perkin Trans. I* **1989**, 1631. (d) Hunter, R.; Michael, J. P.; Simon, C. D.; Walter, D. S. *Tetrahedron* **1994**, *50*, 9365. (e) Hunter, R.; Michael, J. P.; Walter, D. S. *Tetrahedron Lett.* **1992**, *33*, 5413. (f) Hunter, R.; Michael, J. P.; Walter, D. S. *Tetrahedron* **1994**, *50*, 9377. (g) Hunter, R.; Michael, J. P.; Walter, D. S. *Tetrahedron Lett.* **1994**, *35*, 5481. (h) Hashimoto, Y.; Mukaiyama, T. *Chem Lett.* **1986**, 755. (i) Hashimoto, Y.; Mukaiyama, T. *Chem Lett. 1986*, 1623. (j) Hashimoto, Y.; Sugumi, H.; Okauchi, T.; Mukaiyama, T. *Chem. Lett.* **1987**, 1691. (k) Hashimoto, Y.; Sugumi, H.; Okauchi, T.; Mukaiyama, T. *Chem. Lett.* **1987**, 1695. (l) Ishihara, T.; Shinozaki, T.; Kuroboshi, M. *Chem. Lett.* **1989**, 1369. (m) Brückner, R.; Huisgen, R. *J. Org. Chem.* **1991**, *56*, 1677. (n) Keiichi, M.; Domon, K.; Tanino, K.; Kuwajima, I. *SYNLETT* **1996**, 157. (o) Takahashi, Y.; Tanino, K.; Kuwajima, I. *Tetrahedron Lett.* **1996**, *37*, 5943. (p) Domon, K.; Masuya, K.; Tanino,K.; Kuwajima, I. *Tetrahedron Lett.* **1997**, *38*, 465. (q) Braish, T. F.; Saddler, J.C.; Fuchs, P. L. *J. Org. Chem.* **1988**, *53*, 3647.
9. All new compounds exhibited satisfactory $^1H$ and $^{13}C$ NMR and IR spectral data as well as satisfactory combustion analysis or high resolution exact mass data.