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Preparation of α-Sulfenyl Enones by Thermal Fragmentation of β-Sulfenyl Enol Triflates

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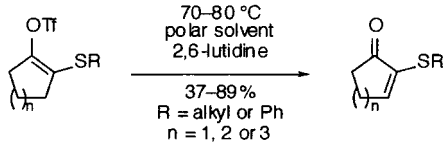
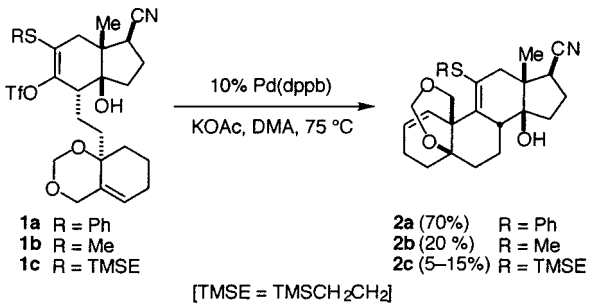
ABSTRACT



The synthetic scope and mechanism of the fragmentation of cyclic β-sulfenyl enol triflates to give α-sulfenyl enones are described. This transformation is the central step in a mild, functional group-tolerant method for preparing α-sulfenyl enones.

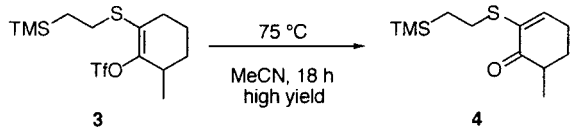
In the context of our recent efforts to synthesize complex cardenolides such as ouabain, we described the intramolecular Heck reaction of β-sulfenyl enol triflate **1a** to give functionalized cardenolide precursor **2a** (Scheme 1).[1] Although this conversion took place smoothly in the phenylthio series, cyclization of the related alkylthio substrates **1b** and **1c** proceeded in low yield.

Scheme 1



After this report, we discovered that **1c** undergoes competitive thermal fragmentation under the reaction conditions depicted in Scheme 1. In an effort to identify this pathway, the reactivity of simplified congener **3** was examined (Scheme 2). We found that simply heating **3** in MeCN *in the absence of a Pd(0) catalyst and base* resulted in the formation of α-sulfenyl enone **4**. To the best of our knowledge, this transformation has not been described in the chemical literature.[2−4] As α-sulfenyl enones have found use

Scheme 2



(1) Hynes, J., Jr.; Overman, L. E.; Nasser, T.; Rucker, P. V. *Tetrahedron Lett.* **1998**, *39*, 4647−4650.

(2) Fragmentation of β-alkoxy enol triflates to give α-alkoxy enones has been observed previously in our laboratories: (a) Rucker, P. V. Ph.D. Dissertation, University of California, Irvine, Irvine, CA, 1999. (b) Old, D. W. Ph.D. Dissertation, University of California, Irvine, Irvine, CA, 1997.

(3) Related fragmentations of 1*H*-indol-3-yl triflates and similar heterocycles have been described; see: (a) Edstrom, E. D.; Yu, T. *J. Org. Chem.* **1995**, *60*, 5382−5383. (b) Malapel-Andrieu, B.; Merour, J. *Tetrahedron Lett.* **1998**, *39*, 39−42.

(4) For a review of reactions induced by triflic anhydride, see: Baraznenok, I. L.; Nenajdenko, V. G.; Balenkova, E. S. *Tetrahedron* **2000**, *56*, 3077−3119.

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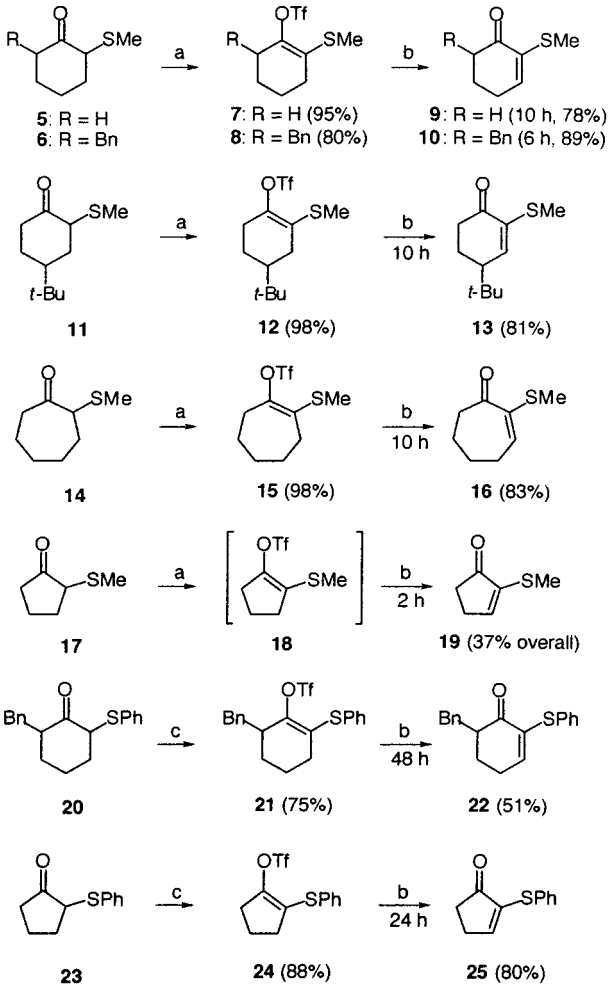
in the synthesis of complex organic molecules[5] and their preparation typically involves oxidative and/or acidic conditions,[6] we decided to investigate further the mild generation of these intermediates from β-sulfenyl enol triflate precursors. The results of these studies are presented herein.

The cyclic β-sulfenyl enol triflates used in our studies were prepared from the corresponding α-sulfenyl ketones[7,8] by enolization with KHMDS in THF at −78 °C and subsequent trapping of the potassium enolate with $PhNTf_2$ or 2-[*N*,*N*-bis(trifluoromethylsulfonyl)amino]-5-chloro-pyridine (Comins' reagent) (Scheme 3).[1,9] With the exception of cyclopentanone-derived enol triflate **18**, these intermediates were moderately stable oils, isolated in yields ranging from 68 to 98%.[10]

Conditions for the thermal fragmentation step were optimized using cyclohexenyl triflate **8** (Scheme 3). Initial experiments showed that the conversion of **8** to α-sulfenyl ketone **10** was the cleanest in the presence of an added base; 2,6-lutidine was found to be suitable for this purpose. A variety of solvents were examined for this reaction: heptane, PhH, PhMe, EtOAc, 1,4-dioxane, DME, 2-butanone, 1,2-dichloroethane, MeCN, *N*,*N*-dimethylacetamide, DMF, DMSO, and EtOH.[11] With the exception of EtOH, the reaction proceeded cleanly in all solvents examined.[12] The conversion of **8** to **10** was fastest in polar aprotic solvents, with the rate of conversion being highest in DMSO and MeCN. Utilization of DMSO as the solvent gave complete conversion of **8** to **10** within 10 h at temperatures between 70 and 80 °C.

Scheme 3[a]



[a] Conditions: (a) KHMDS, $PhNTf_2$; (b) 2,6-lutidine, DMSO, 80 °C; (c) KHMDS, Comins' reagent.

The scope of this synthesis of cyclic α-sulfenyl enones was explored using thermolysis conditions found to be optimal for the conversion of **8** to **10**: 80 °C in DMSO containing 1.5 equiv of 2,6-lutidine. As summarized in Scheme 3, cyclohexenyl and cycloheptenyl α-methylthio enones (**9**, **10**, **13**, and **16**) were formed in good yields. Alkyl substitution was tolerated both adjacent to the triflate and at the allylic position of the enone product. The conversion of 2-(methylthio)cyclopentanone (**17**) to α-sulfenyl enone **19** was low yielding, undoubtedly reflecting the instability of triflate **18**. When the sulfur substituent was phenyl, the thermal fragmentation step was slower. For example, 48 h was required for the conversion of β-phenylthio enol triflate **21** to enone **22**.[13] This conversion was not as clean as the analogous transformation in the methylthio series (**8** → **10**). However, the attenuated reactivity of β-phenylthio enol triflate intermediates proved to be advantageous in the cyclopentenyl series. Whereas methylthio triflate **18** could not be isolated, phenylthio congener **24** was isolated without incident. Subsequent thermolysis of **24** in DMSO at 80 °C for 24 h resulted in the production of 2-(phenylthio)-cyclopenten-2-one (**25**) in 80% yield.

Acetonitrile is also a convenient solvent for the thermal fragmentation step. For example, cyclohexenyl triflate **26** was converted to α-methylthio cyclohexenone **27** within 12 h at

(5) Selected examples: (a) Aratani, M.; Dunkerton, L. V.; Fukuyama, T.; Kishi, Y.; Kakoi, H.; Sugiura, S.; Inoue, S. *J. Org. Chem.* **1975**, *40*, 2009−2011. (b) Yechezkel, T.; Ghera, E.; Ostercamp, D.; Hassner, A. *J. Org. Chem.* **1995**, *60*, 5135−5142. (c) Lebsack, A. D.; Overman, L. E.; Valentekovich, R. J. *J. Am. Chem. Soc.* **2001**, *123*, 4851−4852.

(6) Acidic: (a) Monteiro, H. J. *J. Org. Chem.* **1977**, *42*, 2324−2326. Vankar, Y. D.; Kumaravel, G.; Bhattacharya, I.; Vankar, P.; Kaur, K. *Tetrahedron* **1995**, *51*, 4829−4840. (b) Guaciaro, M. A.; Wovkulich, P. M.; Smith, A. B., III. *Tetrahedron Lett.* **1978**, *47*, 4661−4664. Oxidative: (c) Tomoeda, M.; Inuzuka, M.; Furuta, T.; Shinozuka, M. *Tetrahedron* **1968**, *24*, 959−974. Tobias, M. A.; Strong, J. G.; Napier, R. P. *J. Org. Chem.* **1970**, *35*, 1709−1711. (d) Sugihara, Y.; Wakabayashi, S.; Saito, N.; Murata, I. *J. Am. Chem. Soc.* **1986**, *108*, 2773−2775. Oxidative and acidic: (e) Monteiro, H. J.; Gemal, A. L. *Synthesis* **1975**, 437−438.

(7) (a) 2-(Methylthio)cycloalkanones were obtained from commercial sources or were prepared according to the procedure of Scholz, D. *Synthesis* **1983**, 944−945.[7] (b) 2-(Phenylthio)cycloalkanones were prepared according to the procedure of Trost, B. M.; Massiot, G. S. *J. Am. Chem. Soc.* **1977**, *99*, 4005−4412.

(8) *A serious explosion occurred when preparing $MeSSO_2Me$ according to the procedure described in ref 6a.* Alternative methods for the preparation of this reagent should be utilized; see: Chemla, F.; Karoyan, P. *Org. Synth.* **2000**, *78*, 99−103 and references cited therein.

(9) (a) Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1992**, *33*, 6299−6302. (b) Compounds **21** and **24** proved to be difficult to purify when prepared using $PhNTf_2$.

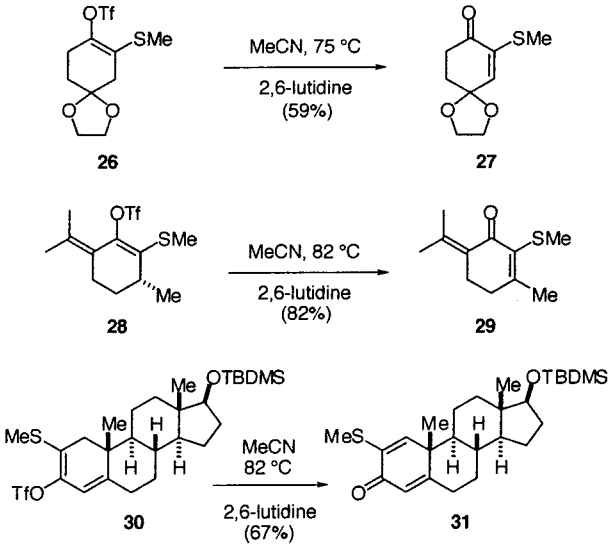
(10) These delicate intermediates could be stored for several weeks as solutions in pentane at −20 °C.

(11) These experiments were run at 80 °C in the presences of ca. 5 equiv of 2,6-lutidine for 4 h; conversion was assessed by ^1H NMR analysis of crude reaction products.

(12) A complex mixture of products that included **10** was formed in EtOH; no attempt was made to identify the other components.

(13) The greater thermal stability of α-phenylthio than α-methylthio enol triflates explains why Heck cyclization of **2a** suceeded, whereas the related cyclization of **2b** was low yielding.[1]

Scheme 4

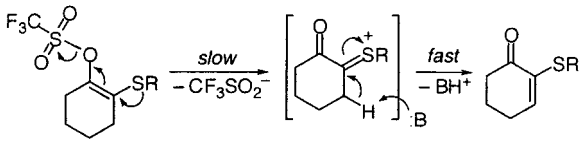


75 °C in MeCN (Scheme 4). Although this conversion also proceeded cleanly in DMSO, the use of more volatile MeCN facilitated isolation of the α-sulfenyl enone product. Thermal fragmentation of pulegone-derived enol triflate **28** in refluxing MeCN provided dienone **29** in 82% yield, a conversion illustrating that tetrasubstituted double bonds can be formed by this method. Testosterone derivative **30** was also converted in useful yield (67%) to dienone **31** in refluxing MeCN. These latter examples demonstrate the utility of this method for forming cross-conjugated dienones that contain an α-methylthio substituent.

To gain further mechanistic insight into the conversion of *β*-sulfenyl enol triflates to α-sulfenyl ketones, the kinetics of the transformation of *β*-sulfenyl enol triflate **8** to α-sulfenyl enone **10** were investigated. This conversion was found to be first order in **8** and zero order in 2,6-lutidine.[14] These data, and the observations that the formation of α-sulfenyl ketones from *β*-sulfenyl enol triflates is faster in more polar solvents and that methylthio triflates fragment more rapidly than their phenylthio congeners,[15] are consistent with an E_1 mechanism (Scheme 5).[16]

(14) See Supporting Information for details.

Scheme 5



In summary, a new sequence for converting cyclic ketones to α-sulfenyl enones has been established.[17] The key step in this method is thermal fragmentation of a *β*-sulfenyl enol triflate intermediate to generate the α-sulfenyl enone product. As a result of the mild nature of this redox fragmentation step, the method should be particularly useful for preparing acid- and oxidant-sensitive α-sulfenyl enones. This study also highlights a potential limitation in employing enol triflates containing electron-releasing groups at the *β*-position in metal-catalyzed cross-coupling reactions.

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Supporting Information Available: Experimental procedures and characterization data for new compounds and details of kinetic investigations of the conversion of **8** to **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Phenylthio ($\sigma_p^+ = -0.55$) is a weaker electron donor than methylthio ($\sigma_p^+ = -0.60$); see: Hansch, C.; Leo, A. *Substituent Constants for Correlation Analysis in Chemistry and Biology*; Wiley & Sons: New York, 1979; pp 87 and 133.

(16) Similar mechanisms were proposed for related conversions of *β*-aza enol triflates.[3]

(17) This sequence might well be useful for preparing acyclic α-sulfenyl enones; however, reaction conditions would likely need to be modified. We found the enol triflate derived from 1,5-diphenyl-2-phenylthio-3-pentanone to be quite labile and its fragmentation to 1,5-diphenyl-2-phenylthio-1-penten-3-one not to be clean under the conditions (MeCN) reported herein.