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Readily Prepared 3-Chloro-1-(phenylthio)propene, a Versatile Three-Carbon Annulating Agent

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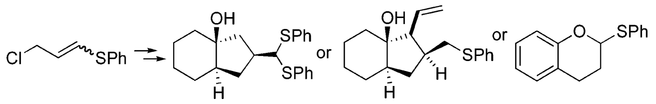
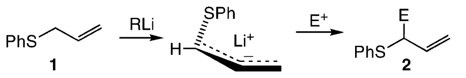
ABSTRACT



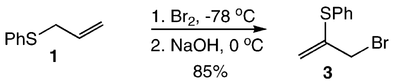
3-Chloro-1-(phenylthio)propene, simply generated by chlorination of commercial allyl phenyl sulfide, is a versatile 3-carbon annulating agent for ketones and phenols.

Allyl phenyl sulfide **1** and a variety of analogues have been widely used, after deprotonation, as nucleophiles, mainly to generate substituted allyl phenyl sulfides **2** (eq 1).[1]



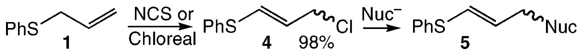
(1)

In a recent publication,[2] our groups reported a one pot conversion of allyl phenyl sulfide, via an interesting rearrangement, into a versatile electrophile **3** that is particularly useful as a three-carbon annulating agent.



(2)

In 1975, the American laboratory reported[3] that allylic phenyl sulfides such as **1** are readily chlorinated by *N*-chlorosuccinimide (NCS) or trichlorisocyanuric acid (Chloreal) to 3-chloro-1-(phenylthio)propenes such as **4** (eq 3). NCS is not as reactive and far more expensive than Chloreal but it is more highly stereoselective for the trans product. In the same paper, both stereoisomers were shown to be capable of undergoing nucleophilic attack by organometallic reagents mainly to directly displace the chloride group to provide products such as **5**. Subsequent publications reported similar displacements with a variety of nucleophiles.[4] Since vinyl sulfides can be readily converted to aldehydes or ketones,[3,5] reagents such as **4** behave as synthons of α,*β*-unsaturated aldehydes or ketones in a Michael sense.[3] In view of the potential versatility of the nucleophilic substitution products such as **5**, it is rather surprising that the only reported uses are as precursors of aldehydes[3] or thioacetals.[4b]



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(1) Katritzky, A. R.; Piffl, M.; Lang, H.; Anders, E. *Chem. Rev.* **1999**, *99*, 665–722.

(2) Chen, W.; Zhao, X.; Lu, L.; Cohen, T. *Org. Lett.* **2006**, *8*, 2087–2090.

(3) Mura, A. J., Jr.; Bennett, D. A.; Cohen, T. *Tetrahedron Lett.* **1975**, *50*, 4433–4436.

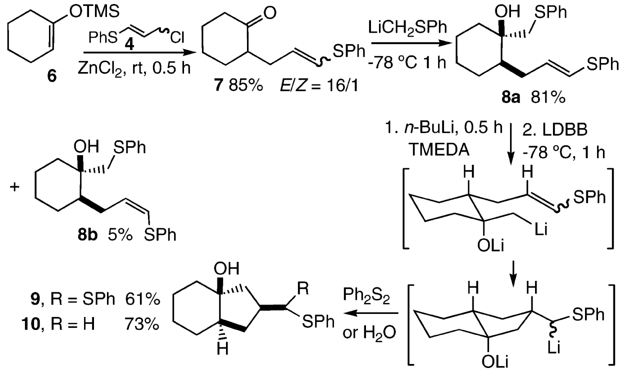
10.1021/ol901818j CCC: $40.75

In the present paper, we demonstrate the utility of **4** as a three-carbon annulating agent by taking advantage of the ability of the activated alkene linkage of **5** to undergo intramolecular additions of organolithiums or phenols. Since divalent sulfur stabilizes both negative and positive charges on the carbon atom to which it is attached, the alkene linkages in compounds such as **5** are quite versatile.

It has been demonstrated that vinyl sulfides undergo reductive lithiation by aromatic radical anions far more slowly than do saturated phenyl thioethers even though the product vinyllithiums are far more stable than alkyllithiums, thus making selective reductive lithiation possible in molecules with both types of phenylthio groups; this has allowed convenient cyclizations to cyclopropanes and cyclobutanes.[6] This concept is herein extended to cyclopentanes.

We have found that α-1-(phenylthio)allylation of cyclohexanone by **4** gives much better yields of **7** when the corresponding enol silyl ether **6** is treated with **4** in the presence of a Lewis acid than when the lithium enolate of cyclohexanone is treated[4b] directly with **4**. Smooth addition[7] of (phenylthio)methyllithium[8] to **7** gave the tertiary alcohols **8a** and **8b**. Deprotonation of this mixture with butyllithium followed by reductive lithiation with lithium 4,4′-di-*tert*-butylbiphenylide (LDBB) generated the alkyllithium group that added to the activated alkene as shown to provide a sulfur-stabilized organolithium capable of sulfenylation to the thioacetal **9** or protonation to the alkyl sulfide **10**. The terminal phenylthio substituent on the alkene linkage of **8a** and **8b** is not essential for cyclization by carbolithiation[9] but it allows greatly enhanced versatility as in the production of **9** (Scheme 1).

Scheme 1. Preparation and Cyclization of the α-Allylated Cyclohexanone Adduct of (Phenylthio)methyllithium



The stereochemistry of **9** was supported by ^{1}H NMR, ^{13}C NMR, and an NOE effect. The *cis* relationship between the hydroxyl group and the CH$_2$SPh group of **10** was established by crystallography (Figure 1).[10]

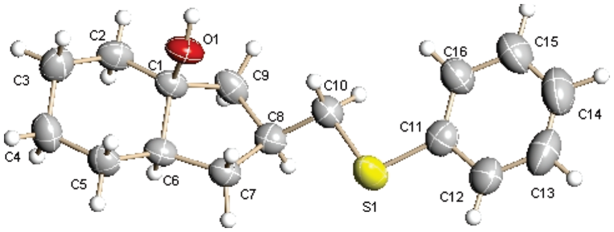
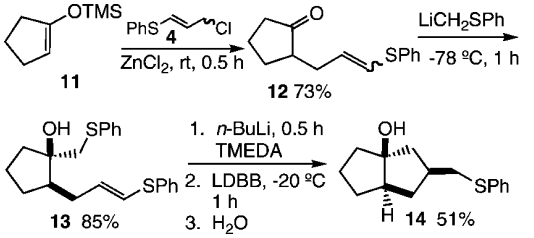


Figure 1. X-ray crystal structure of **10**.

It was anticipated that a similar sequence starting from the trimethylsilyl enol ether **11** of cyclopentanone would be challenging because of the notorious strain of trans-fused diquinanes.[9c] As shown in Scheme 2, α-allylated cyclopentanone **12** and its adduct **13** with (phenylthio)methyllithium were readily obtained. However, after reductive lithiation, no cyclization was observed at −78 °C. Gratifyingly, at −20° cyclization occurred to the diquinane **14**, albeit in lower yield than in the formation of **10** in which the generated 5-membered ring is fused to a 6-membered ring. The trans stereochemistry of **13** and therefore of **14** is assumed on the basis of the high probability that the organolithium attacks the cyclopentanone **12** from the least hindered side as occurs in the case of the addition of the same organolithium to the closely analogous cyclohexanone **7** in Scheme 1.

Scheme 2. Preparation and Cyclization of the α-Allylated Cyclopentanone Adduct of (Phenylthio)methyllithium



A similar sequence starting with the cycloheptanone silyl ether should be particularly useful if successful since it would

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(4) (a) Cohen, T.; Bennett, D. A.; Mura, A. J., Jr. *J. Org. Chem.* **1976**, *41*, 2506–2507. (b) Ritter, R. H.; Cohen, T. *J. Am. Chem. Soc.* **1986**, *108*, 3718–3725. (c) Fitt, J. J.; Gschwend, H. W. *J. Org. Chem.* **1979**, *44*, 303–305.

(5) Mura, A. J., Jr.; Majetich, G.; Grieco, P. A.; Cohen, T. *Tetrahedron Lett.* **1975**, 4437–4440.

(6) Chen, F.; Mudryk, B.; Cohen, T. *Tetrahedron* **1999**, *55*, 3291–3304.

(7) Hannaby, M.; Warren, S. *J. Chem. Soc., Perkin Trans. 1* **1989**, 303–311.

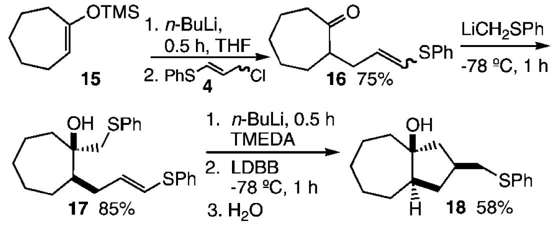
(8) Corey, E. J.; Seebach, D. *J. Org. Chem.* **1966**, *31*, 4097–4099.

(9) Terminal alkenes readily undergo cyclization by intramolecular carbolthiation to generated cyclopenylmethyllithiums. Reviews: (a) Mealy, M. J.; Bailey, W. F. *J. Organomet. Chem.* **2002**, *646*, 59–67. (b) Hogan, A. M. L.; O'Shea, D. F. *Chem. Commun.* **2008**, 3839–3851, Recent papers: (c) Deng, K.; Bensari-Bouguerra, A.; Whetstone, J.; Cohen, T. *J. Org. Chem.* **2006**, *71*, 2360–2372, and citations therein. (d) Sanz, R.; Ignacio, J. M.; Rodriguez, M. A.; Fananas, F. J.; Barluenga, J. *Chem.—Eur. J.* **2007**, *13*, 4998–5008. (e) Groth, U.; Kottgen, P.; Langenbach, P.; Lindenmaier, A.; Schutz, T.; Wiegand, M. *Synlett* **2008**, 1301–1304. (f) Bahde, R. J.; Rychnovsky, S. D. *Org. Lett.* **2008**, *10*, 4017–4020. (g) Tsuchida, S.; Kaneshige, A.; Ogata, T.; Baba, H.; Yamamoto, Y.; Tomioka, K. *Org. Lett.* **2008**, *10*, 3635–3638.

(10) Crystallographic data of **10** (CCDC 278769) can be obtained free of charge from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB 1EZ, UK; email: deposit@ccdc.cam.ac.uk.

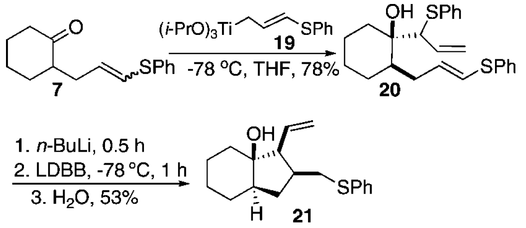
result in the formation of a usefully functionalized hydrazulane, a widespread natural ring system.[11] However, the zinc chloride catalyzed allylation of the enol silyl ether **15** led to an inseparable mixture. The allylation of the lithium enolate, generated by the treatment of **15** with butyllithium, produced **16** in satisfactory yield. Subsequent processing in the usual way did indeed yield the functionalized hydrazulene **18** (Scheme 3). Only the trans alkene **17** could be isolated although a small amount of the cis isomer was probably also formed in the addition.

Scheme 3. Preparation and Cyclization of the α-Allylated Cycloheptanone Adduct of (Phenylthio)methyllithium



To demonstrate the introduction of still more functionality into the cyclized product, **7** was treated with the 1-(phenylthio)allyltitanium reagent **19**, readily prepared[12] by deprotonation of allyl phenyl sulfide followed by transmetalation, to generate **20** (Scheme 4). Deprotonation and reductive lithiation of the latter, as in the case of **8**, produced the highly functionalized bicyclic system **21**. Its stereochemistry was established by crystallography (Figure 2).[13]

Scheme 4. Preparation and Cyclization of the α-Allylated Ketone Adduct of 1-(Phenylthio)allyltitanium



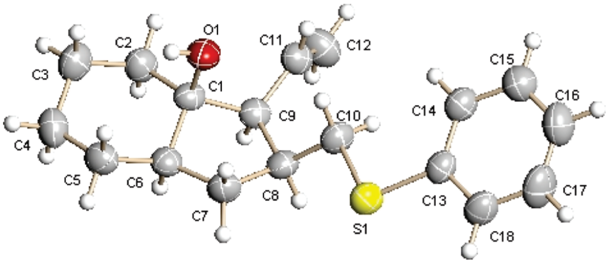
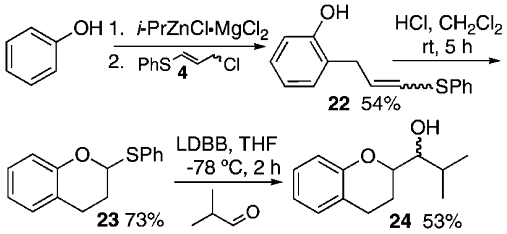


Figure 2. X-ray crystal structure of **21**.

To demonstrate an entirely different type of cyclization afforded by the vinyl sulfide group, namely one depending on the ability of the phenylthio group to stabilize a positive rather than a negative charge, the ortho 3-(phenylthio)allylation of phenol was attempted by treating a zinc salt of phenol with the allylic chloride **4**. The hope was that the zinc ion attached to the oxygen atom would behave as a Lewis acid toward the chloride and remove it in a 6-membered ring transition state to deliver the allylic group mainly or exclusively to the ortho position.[14] In the event, when phenol was deprotonated by *i*-PrZnCl•MgCl$_2$, generated by mixing *i*-PrMgCl and ZnCl$_2$, and the product was treated with **4**, the ortho allylated phenol **22** was indeed isolated in 54% yield. In the presence of acid, the alkene was protonated to a sulfur-stabilized carbocation that was captured by the phenolic group to deliver 2-(phenylthio)chroman **23**[15] in 73% yield. As in the case of other α-(phenylthio)ethers,[16] reductive lithiation generates the α-lithioether; in this case, it was captured by isobutyraldehyde to produce a 1:1 mixture of *syn*-**24a** and *anti*-**24b** in 53% unoptimized yield (Scheme 5).

Scheme 5. Preparation and Cyclization of an *o*-(3-Phenylthio)allylated Phenol



In summary, 3-chloro-1-(phenylthio)propenes such as **4**, readily prepared by chlorination of allyl phenyl sulfide, are useful electrophiles which can be incorporated into the α-position of ketones and the ortho-position of phenols to provide cyclization precursors. For the cyclization step, use is made of the ability of divalent sulfur to stabilize either a

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(11) Heathcock, C. L.; Graham, S. L.; Pirrung, M. C.; Plavac, F.; White, C. T. *The Total Synthesis of Natural Products*, Vol. 5; ApSimon, J., Ed.; J. Wiley and Sons: New York, 1982; pp 333−384.

(12) Ikeda, Y; Furuta, K.; Meguriya, N.; Ikeda, N.; Yamamoto, H. *J. Am. Chem. Soc.* **1982**, *104*, 7663–7665.

(13) Crystallographic data of **21** (CCDC 739965) can be obtained free of charge via from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB 1EZ, UK; email: deposit@ccdc.cam.ac.uk.

(14) The potassium salts of several phenols were reported to undergo ortho-allylation in the presence of various allylic halides and catalytic amounts of zinc chloride but neither other products nor a mechanism were discussed: Bigi, F.; Casiraghi, G.; Casnati, G.; Sartori, G. *Synthesis* **1981**, 310–312. However, a 6-member ring transition state can be surmised from a subsequent review by some of the same authors: Casnati, G.; Casiraghi, G.; Pochini, A.; Sartori, G.; Ungaro, R. *Pure Appl. Chem.* **1983**, *55*, 1677–1688.

(15) The replacement of the phenylthio group of **23** by allyl, Cl, and F as well as its oxidation to a sulfoxide is recorded in the literature but curiously no synthesis of **23** appears. Nishiyama, H.; Narimatsu, S.; Sakuta, K.; Itoh, K. *J. Chem. Soc., Chem. Commun.* **1982**, 459–460. Ringom, R.; Benneche, T. *Acta Chem. Scand.* **1999**, *53*, 41–47.

(16) Cohen, T.; Matz, J. R. *J. Am. Chem. Soc.* **1980**, *102*, 6900–6902. Cohen, T.; Lin, M. *J. Am. Chem. Soc.* **1984**, *106*, 1130–1131.

negative and or a positive charge at the carbon to which the sulfur atom is attached. In view of the fact that various substituted allyl phenyl sulfides can be similarly chlorinated to provide substituted analogues of **4**, this simple annulation protocol should prove quite general.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds as well as crystallographic data for compounds **10** and **21**. This material is available free of charge via the Internet at http://pubs.acs.org.

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