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# 2-Phenylthio-3-bromopropene, A Valuable Synthon, Easily Prepared by a Simple Rearrangement

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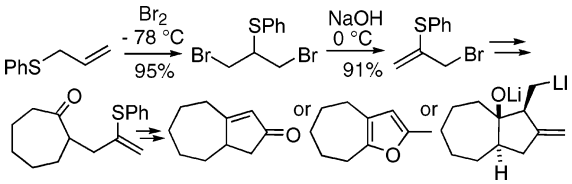
## ABSTRACT



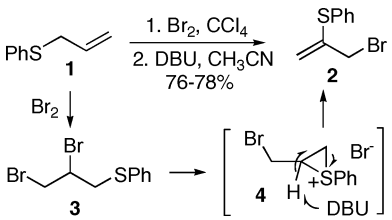

**Treatment of allyl phenyl sulfide with bromine, followed by aqueous sodium hydroxide, provides a good yield of 2-phenylthio-3-bromopropene 2 via a mechanism that is elucidated by isolation of the 1,3-dibromo-2-(phenylthio)propene intermediate 7. Three uses of 2 as an annulating agent for cycloheptanone are illustrated, demonstrating that this reagent is a synthetic equivalent of acetonyl halide and an α-halo vinyllithium. It is also readily converted to the useful synthons 2,3-bis(phenylthio)propene 16 and 2-phenylthio-3-(phenylsulfonyl)propene 17.**

The recently reported[1] presumably[2] one-pot transformation of allyl phenyl sulfide **1** to 2-phenylthio-3-bromopropene **2** (Scheme 1) caught our attention both because of mechanistic considerations and the perceived great synthetic utility of the previously unknown allyl bromide **2**. An analogous transformation occurred with the terminally methylated analogue of **1**, 4-phenylthio-2-butene.[1] In the present paper, we elucidate the mechanism of the transformation and present some uses of **2** that show considerable synthetic utility.

We deemed the suggested mechanism, via **3** and **4**, unlikely partly because the transformation of **4** to **2** appeared to be stereoelectronically unfavorable due to the orthogonal arrangement of the two bonds that are being broken. A mechanism that appeared more likely is shown in Scheme 2. It is reasonable to expect that intramolecular nucleophilic displacement of the bromine cation in the intermediate bromonium ion **5** by the sulfur atom of the phenylthio group[3] would be favored over external displacement by a bromide ion, thus leading to the episulfonium salt **6**. Nucleophilic opening of the three-membered ring by a bromide ion would lead to the dibromide **7** that would be easily dehydrobrominated by DBU to generate the allyl bromide **2**.

Bromination of **1** without treatment of the product with base did indeed yield the predicted intermediate **7** as well as smaller quantities of the vicinal dibromide **3**; the yield

**Scheme 1.** Conversion of Allyl Phenyl Sulfide to 2-Phenylthio-3-bromopropene and Literature Mechanism

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(1) Masuyama, Y.; Sano, T.; Oshima, M.; Kurusu, Y. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 1679−1690.

(2) A number of experimental details were not included in ref 1.

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was essentially quantitative. As a perusal of Table 1 indicates, the selectivity in favor of **7** increases as the temperature is lowered, and the reaction is very highly selective at −78 °C, producing a 95% yield of **7** as a 24:1 mixture with **3**. Even at reflux in $CCl_4$, **7** is favored over **3** by 3.4:1. However, when **7** was heated at reflux in $CDCl_3$ for 2 days, the ratio of **7** to **3** became 0.29 to 1.0. Thus, counterintuitively, but in accord with the mechanism in Scheme 2, **7** is the kinetic product and the thermodynamic product is a mixture of **7** and **3** in approximately the statistical ratio that would be 0.5 to 1.0 in view of the fact that there are two possible arrangements of the substituents on **3** and only one of those on **7**. It is evident that, not surprisingly, the conversion of **6** to **7** is reversible and **6** can occasionally suffer nucleophilic attack by bromide ion at the more substituted position.

**Scheme 2.** Alternative Mechanism of Conversion of Allyl Phenyl Sulfide to 2-Phenylthio-3-bromopropene **2**

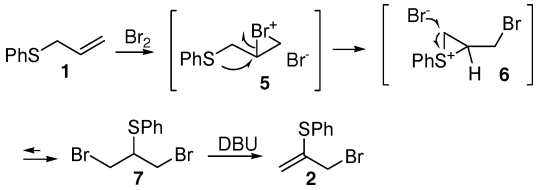
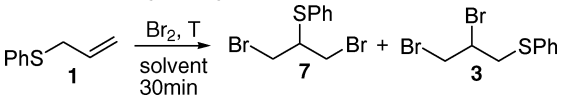



**Table 1.** Effect of Temperature and Solvents on the Bromination of Ally Phenyl Sulfide



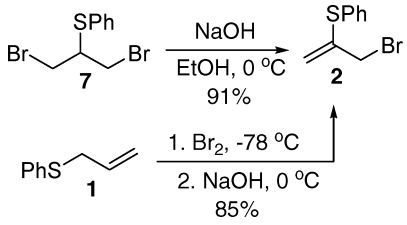

| solvent | $T$, °C | ratio of **7**:**3**[a] |
|---|---|---|
| $CCl_4$ | reflux | 3.4:1 |
| $CCl_4$ | 15 | 4.7:1 |
| $CCl_4$ | 5 | 5.6:1 |
| $CCl_4$ | −15 | 8.8:1 |
| $CH_2Cl_2$ | 5 | 10.3:1 |
| $CHCl_3$ | 5 | 15.0:1 |
| $CHCl_3$ | −55 | 16.6:1 |
| $CH_2Cl_2$ | −78 | 24.0:1 |

[a] HPLC analytical data.

We then turned our attention to modification of the dehydrobromination procedure of **7**. Several bases, including DBU, $K_2CO_3$, and NaOH, were screened. Gratifyingly, it was found that a slurry of NaOH in ethanol at 0 °C led to a 91% yield of 2-phenylthio-3-bromopropene **2** (Scheme 3).

A somewhat simplified procedure, involving adding the solution containing **7**, without isolation of the latter, to the slurry of NaOH produced **2** in a slightly enhanced overall yield (Scheme 3). It should be noted that this expedient method is highly practical because of the simple workup and high yield.[4]

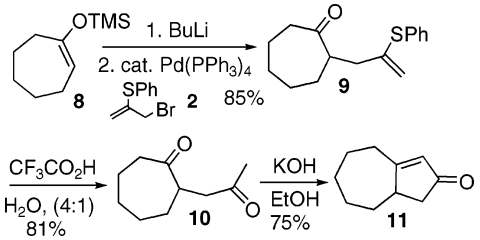
**Scheme 3.** Dehydrobromination of 1,3-Dibromo-1-(phenylthio)propane




In this paper, we concentrate on the use of **2** as a versatile electrophile, although we plan to investigate its reduction to allylmetals,[5] as well.

In Schemes 4−6, we demonstrate the use of **2** as a ketone annulating agent as α-haloketone and α-halovinyllithium equivalents. Other α-haloketone equivalents are available in which an alkoxy group is in place of the phenylthio group of **2**, but these are generally more difficult to prepare.[6] A recent paper indicates how difficult it is to make and use such synthons.[7] To get around this problem in annulations on to ketones, roundabout ways, involving radical cyclizations, have been used.[8]

**Scheme 4.** Allylation of Lithium Enolate of Cycloheptanone and Cyclization of Product to a Cyclopentenone




The Pd-catalyzed allylation of the enolate of cycloheptanone by **2** proceeded in good yield (Scheme 4).[9] Three

(3) 1,2-Rearrangements of phenylthio groups to carbocationic centers: Warren, S. *Acc. Chem. Res.* **2002**, *35*, 401−406.

(4) The procedure is as follows. To a solution of phenyl allyl sulfide (3.2 g, 21 mmol, 1.0 equiv) in 15 mL of $CH_2Cl_2$ at −78 °C was added dropwise a solution of $Br_2$ (1.3 mL, 1.2 equiv, 25 mmol) in 10 mL of $CH_2Cl_2$. The reaction mixture was stirred for 30 min more and then warmed to room temperature. The resulting mixture was added dropwise to a slurry of NaOH (1.30 g, 32 mmol, 1.5 equiv) in 20 mL of ethanol at 0 °C, and the mixture was stirred for 2 h. The mixture was diluted with hexane, filtered, and concentrated. Chromatography on silica with elution by hexane gave 2-phenylthio-3-bromopropenes **2** (4.2 g, 85%) as a colorless liquid. The $^1$H NMR spectrum matched that reported.[1]

(5) There is a brief mention in the original paper of its conversion to an allyltin.[1]

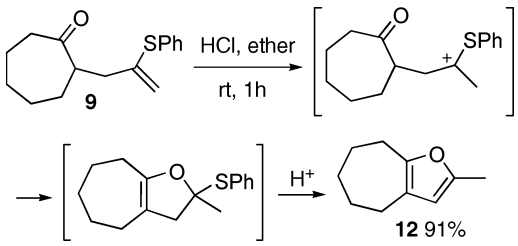
(6) Janicki, S. Z.; Fairgrieve, J. M.; Petillo, P. A. *J. Org. Chem.* **1998**, *63*, 3694−3700 and references therein.

(7) Yasuda, M.; Tsuji, S.; Shigeyoshi, Y.; Baba, A. *J. Am. Chem. Soc.* **2002**, *124*, 7440−7447.

(8) Srikrishna, A.; Viswajanani, R.; Sattigeri, J. A. *Tetrahedron: Asymmetry* **2003**, *14*, 2975−2983.

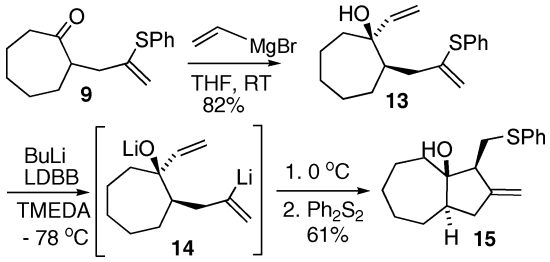
(9) Negishi, E.; Matsushita, H.; Chatterjee, S.; John, R. A. *J. Org. Chem.* **1982**, *47*, 3188−3190.

**Scheme 5.** Conversion of Allylation Product To a Fused Furan




exemplary synthetic uses of the α-allyl ketone product **9** are given. The first of these, also shown in Scheme 4, is aqueous acidic hydrolysis of **9** to yield the known[10] 1,4-diketone **10**, which has been cyclized in base to produce the [7,5]-fused cyclopentenone **11**.[10]

**Scheme 6.** Cyclization of Derived Reductive Lithiation Product with Oxyanionic Assistance

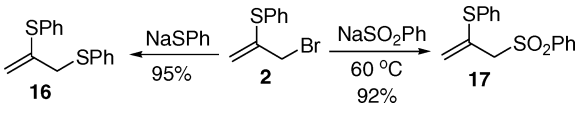



The second use of **9** is acid treatment under *anhydrous* conditions to produce the known[11] fused furan **12** in excellent yield (Scheme 5).[12]

A final use of **9** demonstrates the utility of the allyl bromide **2** as an annulating agent involving reductive lithiation to replace the phenylthio group of a derived product with lithium (Scheme 6). It has been shown that appropriately placed allylic lithium oxyanions greatly assist and stereochemically direct cyclizations to five-membered rings via intramolecular carbolithiation.[13] The allyl alcohol **13** was produced by the addition of the vinyl Grignard reagent to **9**; the same stereochemistry resulted as in the analogous addition[14] to the analogue of **9** lacking the phenylthio group as indicated by the identity of the product of protonation of the dianion **14** to the known[14] allylic alcohol. Deprotonation and reductive lithiation[13] of **13** by lithium 4,4′-di-*tert*-butylbiphenylide (LDBB) generated the vinyllithium **14** which cyclized in the presence of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine[15] to a cyclopentylmethyllithium that was sulfenylated to give 61% of **15** in addition to smaller amounts of protonated **14** and uncyclized starting material. The stereochemistry of **15**, determined by X-ray crystal structure analysis of a derivative (see Supporting Information), is surprising since in all of the many examples of such oxyanionic directed carbolithiation of nonallylic organolithiums the major product has the $CH_2Li$ group trans to the oxyanion.[13] Interestingly, the only previous example which gave any detectable amount (10%) of cis product involved cyclization of a vinyllithium as in the present case. The reason for this discrepancy is presently unknown.

Finally, since allyl phenyl sulfides[16] and sulfones[17] have been proven to be extremely useful synthetic reagents, one can be confident that placing a phenylthio group on the central carbon atom of such systems would greatly increase the versatility of these reagents. This of course can be very easily accomplished with the use of the allyl bromide **2**, as shown in Scheme 7. Padwa has already shown some of the utility of **17** produced by a slightly longer sequence.[18] Bis-2,3-(phenylthio)propene **16** is unknown.

**Scheme 7.** Production of 2-Phenylsulfenylated Allyl Phenyl Sulfides and Sulfones




In summary, a convenient method for preparing 2-phenylthio-3-bromopropene **2** by bromination of allyl phenyl sulfide **1** followed by base treatment is described, and the

(10) Jacobson, R. M.; Raths, R. A.; McDonald, J. H., III. *J. Org. Chem.* **1977**, *42*, 2545−2549. The diketone **10** was prepared by allylation of the metalloenamine of cycloheptanone with 2-methoxy-3-bromopropene, mixed with byproducts from the difficult preparation of the latter, and subsequent hydrolysis.

(11) Imagawa, H.; Kurisaki, T.; Nishizawa, M. *Org. Lett.* **2004**, *6*, 3679−3681.

(12) α-Acetonyl ketones and their equivalents are known to form such furans upon acid treatment. (a) Gingerich, S. B.; Jennings, P. W. *J. Org. Chem.* **1983**, *46*, 2606−2608. (b) Nienhouse, E. J.; Irwin, R. M.; Finni, G. R. *J. Am. Chem. Soc.* **1967**, *89*, 4557−4558.

(13) (a) Deng, K.; Bensari, A.; Cohen, T. *J. Am. Chem. Soc.* **2002**, *124*, 12106−12107. (b) Deng, K.; Bensari-Bouguerra, A.; Whetstone, J.; Cohen, T. *J. Org. Chem.* **2006**, *71*, 2360−2372.

(14) Avasthi, K.; Salomon, R. G. *J. Org. Chem.* **1986**, *51*, 2556−2562.

(15) Bailey, W. F.; Mealy, M. J.; Wiberg, K. B. *Org. Lett.* **2002**, *4*, 791−794.

(16) (a) Piffl, M.; Weston, J.; Gunther, W.; Anders, E. *J. Org. Chem.* **2000**, *65*, 5942−5950 and citations therein. (b) Warren, S. *Acc. Chem. Res.* **2002**, *35*, 401−406. (c) Freeman, R.; Haynes, R. K.; Loughlin, W. A.; Mitchell, C.; Stokes, J. V. *Pure Appl. Chem.* **1993**, *65*, 647−54. (d) Cohen, T.; Bhupathy, M. *Acc. Chem Res.* **1989**, *22*, 152−161. (e) McCullough, D. W.; Bhupathy, M.; Piccolino, E.; Cohen, T. *Tetrahedron* **1991**, *47*, 9727−9736. (f) Cabral, J. A.; Cohen, T.; Doubleday, W. W.; Duchelle, E. F.; Fraenkel, G.; Guo, B.-S.; Yü, S. H. *J. Org. Chem.* **1992**, *57*, 3680−3684. (g) Cheng, D.; Knox, K. R.; Cohen, T. *J. Am. Chem. Soc.* **2000**, *122*, 412−413. (h) Maercker, A.; Jaroschek, H.-J. *J. Organomet. Chem.* **1976**, *116*, 21−37. (i) Cheng, D.; Zhu, S.; Yu, Z.; Cohen, T. *J. Am. Chem. Soc.* **2001**, *123*, 30−34. (j) Denmark, S. E.; Weber, E. J.; Wilson, T. M.; Willson, T. M. *Tetrahedron* **1989**, *45*, 1053−1065 and citations therein (EN 1262). (k) Keck, G. E.; Cressman, E. N. K.; Enholm, E. J. *J. Org. Chem.* **1989**, *54*, 4345−4349 and citations therein. (l) Evans, D. A.; Andrews, G. C. *Acc. Chem. Res.* **1974**, *7*, 147−155. (m) Kosarych, Z.; Cohen, T. *Tetrahedron Lett.* **1982**, *23*, 3019−3022 and citations therein. (n) Cohen, T.; Kosarych, Z. *J. Org. Chem.* **1982**, *47*, 4005−4007. (o) Mura, A. J., Jr.; Bennett, D. A.; Cohen, T. *Tetrahedron Lett.* **1975**, 4433−4436.

(17) (a) Simpkins, N. S. *Sulphones in Organic Synthesis*; Pergamon: New York, 1993. (b) Deng, K.; Chalker, J.; Yang, A.; Cohen, T. *Org. Lett.* **2005**, *7*, 3637−3640.

(18) Padwa, A.; Bullock, W. H.; Dyszlewski, A. D. *J. Org. Chem.* **1990**, *55*, 955−964.

mechanism of the transformation is elucidated based on the isolation and subsequent dehydrobromination of the 1,3-dibromo-2-(phenylthio)propane intermediate **7**. Three uses of 2-phenylthio-3-bromopropene **2** as an annulating agent for cycloheptanone are illustrated, two of these demonstrating that this reagent is an acetonyl halide equivalent and the other that it is an α-halo vinyllithium equivalent. The reagent is also readily converted to the useful synthons 2,3-bis-(phenylthio)propene **16** and 2-phenylthio-3-(phenylsulfonyl)-propene **17**.

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

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