3642-51-1; **34a**, 85067-50-1; **34b**, 3642-25-9; **35a**, 85067-51-2; **35b**, 85067-52-3; **36a**, 83187-03-5; **36b**, 83187-08-0; **36c**, 83187-06-8; **37a**, 83213-89-2; **37b**, 83214-18-0; **37c**, 83213-90-5; **38a**, 83187-02-4; **38b**, 85067-53-4; **38c**, 83187-05-7; **39**, 85067-54-5; **40**, 85067-55-6; **41a**, 85067-56-7; **41b**, 85067-57-8; **42**, 85067-58-9; **43**, 85067-59-0; **44**, 85067-60-3; **45a**, 85067-61-4; **45b**, 85067-62-5; **45b** debromo derivative, 85067-63-6; **46a**, 83187-04-6; **46b**, 85067-64-7; **46c**, 83187-07-9; **50**, 83187-09-1; **51**, 83187-10-4; **52**, 83187-11-5.

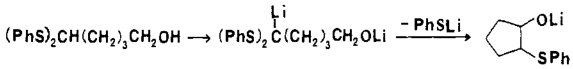
Chemoselective Behavior of Enolate Carbenes Derived from Dianions of Enol Thioacetals

Theodore Cohen* and Lin-Chen Yu

Contribution from the Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260. *Received August 23, 1982*

Abstract: Evidence is provided for the generality of the newly enunciated concept that the normally stable lithio derivatives of diphenyl thioacetals decompose cleanly to carbenes when another negative charge is present nearby in the same molecule; furthermore, in contrast to conventional carbenes, these carbenes can be highly selective in their reactions which are shown to be determined by the nature of the second anionic site and its juxtaposition with respect to the carbenic carbon atom. When the lithium enolate produced by β-addition of tris(phenylthio)methyllithium to 2-cyclohexenone is treated with *sec*-butyllithium at −50 °C, sulfur–lithium exchange occurs and the resulting double conjugate base of an enol thioacetal, upon being warmed to 0 °C, decomposes to a lithium dienolate which is believed to arise by a 1,2-hydrogen transfer in the intermediate enolate carbene. A similar sequence starting with (−)-carvone results in the production of a bicyclo[4.1.0] system formally resulting from the addition of PhSCH across the enone double bond. The difference in behavior in the two systems is rationalized on the basis of conformational differences. Cyclopentenone gives both types of products.

The following previously unrecognized principle, which can be of considerable mechanistic and synthetic significance, has recently been enunciated: Normally stable lithio salts of diphenyl thioacetals decompose to carbenes when they are generated in a molecule with a second anionic site nearby and the anionic moiety of the resulting carbene anion may be influential in determining the reaction course of the carbene.[1] The significance of the concept is that it may allow the ready generation of a usefully substituted and selectively reactive carbene in a variety of types of molecules. One example of the unconventional chemistry engendered by this new concept is the ring closure shown in eq 1 in which the carbene formed by loss of thiophenoxide ion from **1** apparently inserts into the weak alkoxide CH bond.[1]

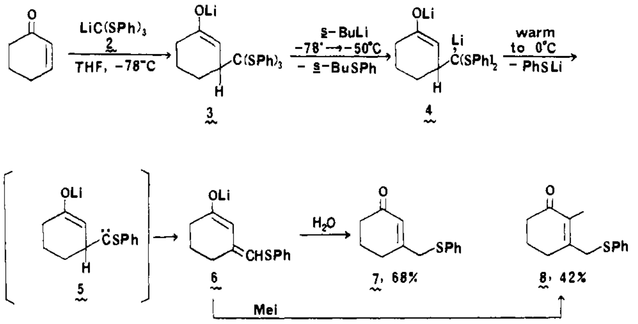


(1)

We now demonstrate the validity of this principle of carbene generation in the case of a new type of conveniently prepared dianion, formally the double conjugate base of a molecule containing both diphenyl thioacetal and ketone functions, and we provide striking illustrations that, in sharp contradistinction to conventional carbenes, the carbenoid carbon atoms of the enolate carbenes produced from these dianions can be remarkably selective in their intramolecular reactions while maintaining high reactivity; *their reactions appear to be totally determined by the disposition of the anionic site with respect to the carbene.*

When the lithium enolate **3** (Scheme I), produced by the addition of tris(phenylthio)methyllithium (**2**) to 2-cyclohexenone at −78 °C,[2,3] is treated with *sec*-butyllithium and the solution is warmed to −50 °C, clean sulfur–lithium exchange[1] occurs to produce the dianion **4**, which can be detected by protonation and by reaction with other electrophiles as will be detailed in a separate report. When the solution of **4** is warmed to 0 °C, the dianion is smoothly converted to the lithium dienolate **6**. The latter, upon protonation, provides a good yield of 3-((phenylthio)methyl)-2-cyclohexenone (**7**) and, upon treatment with methyl iodide, yields mainly **8**, the monomethyl derivative of **7**, along with some dimethylation product.[4] The formation of **8** constitutes a one-pot α,β-disubstitution of cyclohexenone.

Scheme I



The dienolate **6** is the product expected from the insertion of the carbenoid carbon atom of **5** into the adjacent CH bond. Although, such 1,2-hydrogen transfers are the most common mode of reaction of carbenes which are uncomplexed to transition metals,[5,6] they were not noted in the carbene anions which were generated previously[1] presumably because other reactions, in which the anionic center plays a dominating role, are far faster than the 1,2-transfer. In the case of **5**, the 1,2-transfer *is* dictated by the negative charge; in fact this transfer should be recognized as a

---

(1) Cohen, T.; Ritter, R. H.; Ouellette, D. *J. Am. Chem. Soc.* **1982**, *104*, 7142.

(2) Manas, A. R.-B.; Smith, R. A. J. *J. Chem. Soc., Chem. Commun.* **1975**, 216. Smith, R. A. J.; Lal, A. R. *Aust. J. Chem.* **1979**, *32*, 353.

(3) Cohen, T.; Nolan, S. M. *Tetrahedron Lett.* **1978**, 3533.

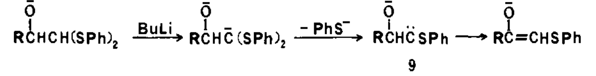
(4) (a) The dimethylation appeared to occur largely at the 2-position, but the product was obtained impure and was not completely characterized. (b) Remarkably, the lithium dienolate **6** is inert toward reaction with the carbonyl reagents, carbon dioxide, propanal, and benzaldehyde; the products of these reactions are presumably thermodynamically unstable with respect to the reactants.

(5) Reviews of carbenes: (a) Wulfman, D. S.; Poling, B. In "Reactive Intermediates"; Abramovitch, R. A., Ed.; Plenum Press: New York, 1980; Vol. 1. (b) Kirmese, W. "Carbene Chemistry", 2nd ed.; Academic Press: New York, 1971. (c) Moss, R.; Jones, M. "Carbenes"; Wiley: New York, 1973; Vol. 1.

(6) Jones, W. M. In "Rearrangements in Ground and Excited States"; de Mayo, P., Ed.; Academic Press: New York, 1980; Vol. 1. Schaefer, H. F., III. *Acc. Chem. Res.* **1979**, *12*, 288.

0002-7863/83/1505-2811$01.50/0

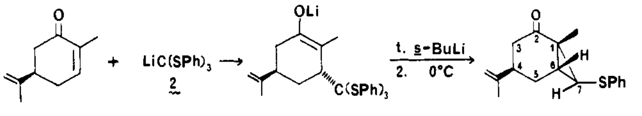
vinylogue of the 1,2-transfer which, according to our interpretation,[1] occurs in the reaction described by Kuwajima and Kurata[7] (eq 2). The CH bond, which is the target of the insertion in **5**,



$$\mathrm{R\overset{\bar{O}}{C}HCH(SPh)_2 \xrightarrow{BuLi} R\overset{\bar{O}}{C}H\bar{C}(SPh)_2 \xrightarrow{-PhS^-} R\overset{\bar{O}}{C}H\ddot{C}SPh \longrightarrow R\overset{\bar{O}}{C}{=}CHSPh} \quad (2)$$

is a weak bond in the same sense that the analogous bonds in **1** and **9** are weak.[1]

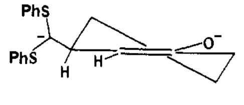
Treatment of (−)-carvone (**10**) with **2** at −78 °C followed by



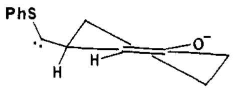
10 **11** **12**, 76%

the addition of *sec*-butyllithium and warming to 0 °C gives an entirely different result. The 7-*exo*-(phenylthio)bicyclo[4.1.0]-heptan-2-one **12** is produced cleanly.[8] It was immediately apparent that **12** was not the structural analogue of **7**. Whereas the infrared spectrum of the latter exhibits a conjugated carbonyl absorption at 1660 cm^{-1}, that of **12** shows a carbonyl absorption at 1690 cm^{-1}, very close to the position (1695 cm^{-1}) of the carbonyl absorption of the des(phenylthio) analogue of **12**.[9] Furthermore, the ^{1}H NMR spectrum of **12** displays no 2-proton singlet at δ 3.6, for protons on the sulfur-bearing carbon atom, as does **7**, and the peak for the methyl group at the 1-position of **12** occurs at δ 1.376 instead of the vicinity of 1.6 as expected of a methyl group attached to a vinyl carbon atom. The major evidence for the structure of **12** was derived from its 300-MHz ^{1}H NMR spectrum and that of is 3,3-dideuterio derivative which was prepared by base-catalyzed exchange. By the use of extensive decoupling experiments, all of the apparent coupling constants could be assigned. The isopropenyl group was assigned the equatorial conformation because the coupling constants between the protons on carbon atoms 4 and 5 are 11.3 and 4.0 Hz. The C-6 proton was assigned the equatorial conformation on the basis of its coupling constants (4.3 and 2.6 Hz) with the protons on C-5. The phenylthio group was assigned the exo orientation on the basis of the coupling of 5.1 Hz for the protons on C-6 and C-7; both the exo and endo analogues, lacking the isopropenyl group and the C-1 methyl group, are known.[10] The ^{13}C NMR spectrum of **12** (see Experimental Section) is also completely compatible with the assigned structure.

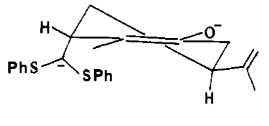
Once again, it is demonstrated that carbene anions can be highly selective in their reactions, that they can generate unique chemistry, and that they are reactive enough to produce strained rings, a fact that should enhance their synthetic utility. The explanation of the difference in behavior of the carbene anions derived from **3** and **11** is most instructive. The dianion precursor, **4**, of **5** would certainly be expected to exist almost completely in the conformation **4a** in which the anionic 3-substituent assumes the quasi-equatorial position. The CH bond adjacent to the carbon atom which is to become the carbene is thus in the quasi-axial conformation, approximately parallel to the π orbital of the enolate system; this bond is thus a true vinylogue of the carbinol CH bond of **9** and is indeed activated by the negatively charged π system resulting in a very rapid insertion into it by the carbene carbon atom of **5a**. Conjugate addition to (−)-carvone (**10**) occurs from the side opposite the isopropenyl group, a well-precedented result,[11] to produce **11**, which is converted to the dianion **13** in which the 3-substituent assumes a quasi-axial conformation in order to minimize the allylic 1,2-repulsion[12] between this substituent and the 2-methyl group and to allow the isopropenyl group to assume the equatorial conformation; the CH bond adjacent to the carbenic carbon atom of the carbene anion **14**, arising from **13**, is thus quasi-equatorial, lying approximately in the plane of the π system, and is thus not specially activated toward insertion. On the other hand, the stereoelectronic arrangement in **14** is almost ideal for interaction of the carbenic center with the electron-rich π system.



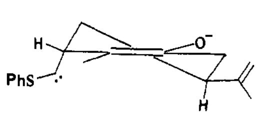
4a



5a

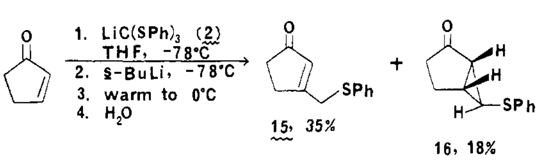


13



14

The reaction of **2** with 2-cyclopentenone at −78 °C followed by treatment with *sec*-butyllithium and warming to 0 °C produces both the 1,2-H transfer product **15** and the bicyclic product **16**, the analogue of **12**. On the basis of the above analysis, this result is not unexpected since the bonds connecting the substituents to C-3 are less nearly parallel with the π system than are quasi-axial bonds in cyclohexenes and more nearly parallel with the π system than are quasi-equatorial bonds in cyclohexenes.



15, 35% **16**, 18%

It is becoming increasingly clear that the new principle of carbene generation is quite general and that the resulting carbene anions are not only reactive but frequently highly selective with the reaction course being determined by the nature of the negatively charged site and its juxtaposition with respect to the carbenic site. Because of the ease of incorporation of the thioacetal anionic function into molecules and the great variety of possible negatively charged sites available, this concept seems destined to provide the means of performing a great variety of novel chemical transformations.

Carbene anions constitute a newly recognized class of reactive intermediates with the potential for diverse molecular reorganizations. Presumably, their novel reactivity patterns would also be manifested in carbene anions which possess substituents at the carbenic site which are different from those that we have used so far. It is very likely that such species will be available by applying conventional carbene-generating techniques to substrates possessing both the carbene progenitor and a negatively charged site. In any event the modes of production and reactions of carbene anions should provide a fertile field for synthetic,[13] mechanistic, and theoretical study.

Experimental Section

Formation and Capture of Dienolate 6. To a solution of 0.547 g (1.61 mmol) of tris(phenylthio)methane (**2**)[14] in 7.5 mL of dry THF, under argon at −78 °C, was added 1.09 mL (1.69 mmol) of a 1.55 M solution of *n*-butyllithium in hexane. The mixture was stirred for 30 min, 2-cyclohexenone (0.155 mL, 1.60 mmol) was added, and stirring was continued for another 2.5 h. The light yellow solution turned orange-red upon the addition of 1.47 mL (1.69 mmol) of a 1.15 M solution of *sec*-butyllithium in cyclohexane at −78 °C. The mixture was warmed to 0 °C, stirred at that temperature for 5 h, and quenched with 5 mL of

---

(7) Kuwajima, I.; Kurata, Y. *Chem. Lett.* **1972**, 291.

(8) Once again the intermediate dianion can be detected by quenching with water at −50 °C. Other chemistry of such dianions will be detailed in a subsequent paper.

(9) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353. See also ref 10.

(10) Schöllkopf, U.; Lehmann, G. J.; Paust, J.; Härtl, H.-D. *Chem. Ber.* **1964**, *97*, 1527.

(11) Rocquet, F.; Sevin, A.; Chodkiewicz, W. *Tetrahedron Lett.* **1971**, 1049. See also: Narayanaswamy, M.; Sathe, V. M.; Rao, A. S. *Chem. Ind. (London)* **1969**, 921.

(12) Johnson, F. *Chem. Rev.* **1978**, *68*, 375.

(13) For example, we have plans to utilize **12** in another project involving total synthesis of optically active hydrazulenes.

(14) Seebach, D.; Geiss, K. H.; Beck, A. K.; Graf, B.; Daum, H. *Chem. Ber.* **1972**, *105*, 3280.

water. The mixture was partitioned between ether and water and the aqueous phase was extracted with ether (3 × 25 mL). The combined organic extract was washed with 10 mL of water and with brine, dried (sodium sulfate), and concentrated in vacuo to provide 0.635 g of crude product which when subjected to flash chromatography (silica gel, elution with a solution of 83 mL of ethyl acetate in 117 mL of hexanes) gave pure 3-((phenylthio)methyl)-2-cyclohexenone (**7**, R_f 0.36) as a colorless oil: ^{1}H NMR ($\mathrm{CDCl_3}$) δ 1.980 (m, 2 H, $\mathrm{COCH_2}CH_2$), 2.326 (t, 2 H, $\mathrm{CO(CH_2)_2}CH_2$), 2.454 (t, 2 H, $\mathrm{COCH_2}$), 3.603 (s, 2 H, $\mathrm{CH_2S}$), 5.762 (s, 1 H, vinyl), 7.322 (m, 5 H, arom); IR (neat) 1660 (CO), 1620 (C=C) cm^{-1}; mass spectrum (15 eV), *m/e* 218 ($\mathrm{M^+}$, 100), 110 ($\mathrm{PhSH^+}$, 37), 109 ($\mathrm{M^+}$ − PhS, 13), 108 ($\mathrm{M^+}$ − PhSH, 12); exact mass calcd for $\mathrm{C_{13}H_{14}OS}$, 218.0765; found, 218.0765.

In a similar experiment starting with 1.66 mmol of **2**, methyl iodide (0.60 mL, 9.6 mmol) (instead of water) was added to the dienolate at −78 °C, and the mixture was allowed to warm to 25 °C and then stirred at that temperature over night. The mixture was stirred with 5 mL of water and worked up as above to give two chromatographic fractions. One of these (R_f 0.35) consisted of a 42% yield of pure 2-methyl-3-((phenylthio)methyl)-2-cyclohexenone (**8**): ^{1}H NMR ($\mathrm{CDCl_3}$) δ 1.542 (br s, 3 H, $\mathrm{CH_3}$), 1.929 (m, 2 H, $\mathrm{COCH_2}CH_2$), 2.381 (t, 2 H, $\mathrm{CO(CH_2)_2}CH_2$), 2.462 (m, 2 H, $\mathrm{COCH_2}$), 3.657 (s, 2 H, $\mathrm{CH_2S}$), 7.388 (m, 3 H, arom), 7.414 (m, 2 H, arom); IR (neat) 1660 (CO), 1630 (C=C) cm^{-1}; mass spectrum (15 eV), *m/e* 232 ($\mathrm{M^+}$, 73), 123 ($\mathrm{M^+}$ − PhS, 61), 110 ($\mathrm{PhSH^+}$, 100); exact mass calcd for $\mathrm{C_{14}H_{16}OS}$, 232.90922; found, 232.0909.

The other fraction (R_f 0.51) consisted of about a 25% yield of an impure material believed to result from methylene of **8** at the 2-position in the basic medium: diagnostic peaks in its ^{1}H NMR spectrum are a gem dimethyl singlet at δ 1.328 (6 H) and a vinyl proton singlet at δ 6.10 (1 H); IR (neat) 1708 (CO), 1660 (C=C) cm^{-1}; mass spectrum (70 eV), *m/e* 246 ($\mathrm{M^+}$, 36), 137 ($\mathrm{M^+}$ − PhS, 100), 109 ($\mathrm{PhS^+}$, 76), 110 ($\mathrm{PhSH^+}$, 47).

7-*exo*-(Phenylthio)-1-methyl-4-isopropenylbicyclo[4.1.0]heptan-2-one (12). To a solution of 0.254 g (0.75 mmol) of tris(phenylthio)methane in 5 mL of THF under argon at −78 °C was added 0.51 mL (0.79 mmol) of a 1.55 M solution of *n*-butyllithium in hexane. The mixture was stirred at −78 °C for 0.5 h, 0.12 mL (0.11 g, 0.76 mmol) of (−)-carvone was added, and stirring was continued for 2 h. *sec*-Butyllithium (0.72 mL, 0.83 mmol), as a 1.15 M solution in cyclohexane, was added at −78 °C whereupon the light yellow solution turned orange-red. The solution was stirred at 0 °C for 5.5 h and then quenched with 2 mL of water. The mixture was worked up as above, using a solution of 113 mL of ethyl acetate and 788 mL of hexanes as eluent, to provide 0.155 g (76%) of **12** (R_f 0.35) as yellow-tinged crystals which could be decolorized by washing with a small quantity of hexanes, mp 121.0–121.5 °C.

The 3,3-dideuterio derivative of **12**, needed in order to assign the peaks and determine the coupling constants in the ^{1}H NMR spectrum of **12**, was prepared by stirring for 14 h at 25 °C a solution containing 0.2 g of **12**, 10 mL of THF, 10 mL of $\mathrm{D_2O}$, and a small quantity of NaOD, prepared by adding sodium to $\mathrm{D_2O}$ under pentane. **12**: ^{1}H NMR ($\mathrm{CDCl_3}$) δ 1.376 (s, 3 H, $\mathrm{CH_3C}$-1), 1.653 (ddd, J = 5.1, 4.3, 2.6 Hz, 1 H, HC-6), 1.726 (s, 3 H, allylic $\mathrm{CH_3}$), 1.977 (ddd, J = 13.9, 11.3, 4.3 Hz, 1 H, axial HC-5), 2.231 (ddd, J = 13.9, 4.0, 2.6 Hz, 1 H, equatorial HC-5), ~2.4 (m, 2 H, $\mathrm{H_2C}$-3), 2.423 (m, 1 H, HC-4), 2.814 (d, J = 5.1 Hz, 1 H, HC-7), 4.743 (br s, 1 H, vinyl), 4.810 (br s, 1 H, vinyl), 7.227 (m, 5 H, arom). These assignments and coupling constants were determined with the aid of the spectrum of the 3,3-dideuterio derivative and extensive decoupling experiments; in the dideuterio derivative the signal for the proton on C-4 became a doublet of doublets, J = 4.0 and 11.3 Hz. The results of decoupling experiments on all of the coupled protons were completely in accord with the structural assignment. ^{13}C NMR (ppm, $\mathrm{CDCl_3}$) 14.526 (q, $C\mathrm{H_3C}$-1), 20.480 (q, allylic $\mathrm{CH_3}$), 26.659 (t, C-5), 28.892 (d, C-6), 30.089 (d, C-7), 35.136 (s, C-1), 37.304 (d, C-4), 42.222 (t, C-3), 110.552 (t, =$\mathrm{CH_2}$), 125.467 (d, *p*-arom), 126.600 (d, *o*-arom), 129.026 (*d*, *m*-arom), 137.018 (s, SC, arom), 146.400 (s, vinyl), 207.387 (s, C-2); IR ($\mathrm{CHCl_3}$) 1690 (CO), 1644 (C=C) cm^{-1}; mass spectrum (15 eV), *m/e* 272 ($\mathrm{M^+}$, 100), 163 ($\mathrm{M^+}$ − PhS, 81), 162 ($\mathrm{M^+}$ − PhSH, 25), 110 ($\mathrm{PhSH^+}$, 23); exact mass calcd for $\mathrm{C_{17}H_{20}OS}$, 272.1235; found, 272.1235.

Preparation and Decomposition of the Dianion Derived from 2-Cyclopentenone. *n*-Butyllithium (4.37 mL of a 1.39 M solution in hexane, 6.07 mmol) was added to a solution of 1.97 g (5.79 mmol) of tris(phenylthio)methane in 25 mL of THF at −78 °C under argon and the solution was stirred for 0.5 h. 2-Cyclopentenone (0.485 mL, 5.79 mmol) was added and the solution was stirred for 1.5 h at −78 °C. *sec*-Butyllithium (5.28 mL of a 1.15 M solution in cyclohexane, 6.07 mmol) was introduced and the mixture was warmed to 0 °C and stirred for 5.5 h. The reaction was quenched with 10 mL of water and the mixture was worked up as above to provide 2.15 g of crude product. Elution of the flash chromatographic column with 1:1 ethyl acetate–hexanes gave 0.42 g (35%) of pure 3-((phenylthio)methyl)-2-cyclopentenone (**15**, R_f 0.40) and 0.22 g (18%) of pure 6-*exo*-(phenylthio)bicyclo[3.1.0]hexan-2-one (**16**, R_f 0.64). **15**: ^{1}H NMR ($\mathrm{CDCl_3}$) δ 2.426 (m, 2 H, $\mathrm{COCH_2}CH_2$), 2.714 (m, 2 H, $\mathrm{COCH_2}$), 3.834 (s, 2 H, $\mathrm{CH_2S}$), 5.936 (br s, 1 H, vinyl), 7.291 (m, 5 H, arom); IR (neat) 1704 (CO), 1620 (C=C) cm^{-1}; mass spectrum (15 eV), *m/e* 204 ($\mathrm{M^+}$, 100), 109 ($\mathrm{PhS^+}$, 16), 95 ($\mathrm{M^+}$ − PhS, 11), 94 ($\mathrm{M^+}$ − PhSH, 15); exact mass calcd for $\mathrm{C_{12}H_{12}OS}$, 204.0609; found, 20.40609. **16**: ^{1}H NMR ($\mathrm{CDCl_3}$) δ 2.153 (m, 6 H, cyclopentyl), 2.588 (dd, J = 2.2, 3.2 Hz, 1 H, HCS), 7.315 (m, 5 H, arom); IR (neat) 1730 (CO); mass spectrum (15 eV), *m/e* 204 ($\mathrm{M^+}$, 56), 162 (M − $\mathrm{CH_2CO}$, 100); exact mass calcd for $\mathrm{C_{12}H_{12}OS}$, 204.0609; found, 204.0609.

Acknowledgment. We thank the National Science Foundation for general support of this work (CHE 7906651) and for providing the funds for purchase of the 300-MHz Bruker NMR instrument used in this study (CHE 7905185). We also thank Dr. Alvin Marcus for recording the mass spectra.

Registry No. 6, 85152-64-3; **7**, 58775-66-9; **8**, 85152-65-4; **10**, 6485-40-1; **12**, 85152-66-5; **12**-*3,3-d*$_2$, 85152-67-6; **15**, 85152-68-7; **16**, 85152-69-8; *n*-BuLi, 109-72-8; *sec*-BuLi, 598-30-1; 2-cyclohexenone, 930-68-7; 2-cyclopentenone, 930-30-3; tris(phenylthio)methane, 4832-52-4.