ELSEVIER

Medium-dependent lithiated side products in the reductive lithiation of allylic phenyl thioethers. Diethyl ether versus tetrahydrofuran

Constantinos G. Screttas,* Georgios A. Heropoulos, Maria Micha-Screttas and Barry R. Steele

Institute of Organic and Pharmaceutical Chemistry, National Hellenic Research Foundation, Vas., Constantinou Avenue 48, Athens 116 35, Greece

Abstract—Diethyl ether is a convenient solvent for the reductive lithiation of allylic phenyl thioethers without the serious complications, which occur when the reaction is carried out in tetrahydrofuran.
© 2005 Elsevier Ltd. All rights reserved.

A recent report by Streiff et al.[1] brought up an important matter concerning the reductive lithiation of allylic-type thioethers. They reported that, in an attempt to reductively lithiate geranyl phenyl thioether under DBB (4,4′-di-*tert*-butylbiphenyl) catalysis and ultrasonic irradiation, extensive lithiation of the sulfide at the allylic carbon occurred instead. It was shown that the lithiated product arose from attack on the thioether of 4-lithioxybutyllithium, which was derived from the reductive ring opening of the THF solvent (Eq. 1).

$$(1)$$
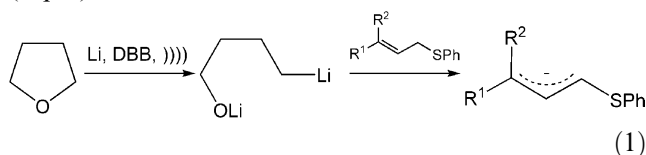
Tetrahydrofuran, which is the conventional medium for carrying out reductive lithiations,[2–4] is a sufficiently strong Lewis base to activate organolithiums towards proton abstraction from carbon acids.[5] Thus, in a number of instances it has been observed that benzylic[2] or allylic[6] type phenyl thioethers, which exhibit considerable carbon acidity, may undergo metalation either by the autogenously produced organolithium reagent or

alternatively, as demonstrated by Streiff et al.,[1] by 4-lithioxybutyllithium. There is evidence that reductive ring opening of THF can take place by a 'silent' reaction as well. This can be inferred from the observation that heating a solution of lithium naphthalene radical anion in THF leads to the formation of 1- and 2-(4-hydroxybutyl)dihydronaphthalenes.[7] This mode of attack on THF differs from the well-known cleavage reaction involving ordinary organolithiums. The latter reagents react by proton abstraction from the α-position of THF and the resulting unstable carbanion undergoes a [2+2] retroaddition to give ethylene and the acetaldehyde enolate.[8] We observed that, after prolonged stirring of lithium metal and a catalytic amount of DBB
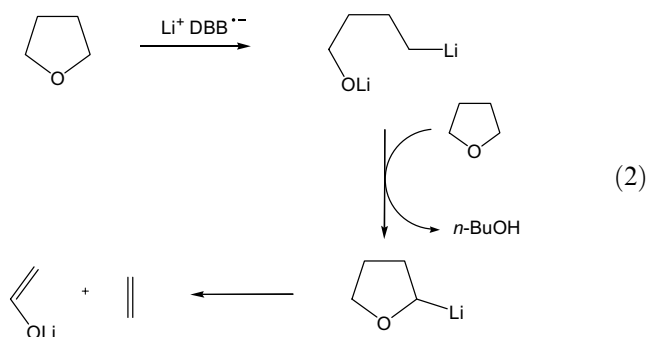

$$(2)$$

in THF, all the lithium was eventually consumed and that on hydrolysis acetaldehyde was produced along with *n*-butanol. These results also imply that $Li^+DBB^{\cdot-}$ decays by a 'silent' reductive ring opening of THF and formation of 4-lithioxybutyllithium, which subsequently decays by proton abstraction from THF (Eq. 2).

Cohen and co-workers have applied the reductive lithiation method extensively to both α-substituted and cyclic allylic phenyl thioethers using the lithium dimethylaminonaphthalene radical anion in THF, apparently without any complications.[9] This lack of complications can be reasonably explained by the higher reactivity of the lithium dimethylaminonaphthalene radical anion as compared to that of $Li^+C_{10}H_8^{\cdot-}$ and the diminished carbon acidity of the thioethers used.

We have reported recently that alkyl phenyl thioethers may be reductively lithiated in diethyl ether,[10] thus extending the range of solvents which can be used for these reactions beyond THF and dimethyl ether.[11] However, even in diethyl ether, the *uncatalyzed* reductive lithiation of benzyl phenyl thioether leads to a mixture of $PhCH_2Li$ and $PhCH(SPh)Li$. Therefore, one can plausibly assume that the metalated thioether derives solely from the attack of benzyllithium on the starting thioether. We reasoned that allylic phenyl thioethers, due to their lower carbon acidity compared to the corresponding benzylic compounds, as well as due to the weaker Lewis basicity of diethyl ether, might be reductively lithiated in diethyl ether without the complications observed when THF is employed as the reaction medium. Here we report our results.

A solution of allyl phenyl sulfide in diethyl ether, on stirring with an excess of lithium chips at ice bath temperature (3–6 °C), initially gave a yellow, cloudy and milky mixture which eventually turned into a thick white emulsion. Carboxylation of this mixture after 2 h afforded 3-butenoic acid in up to 87% yield (see Table 1, entry 1). High yields of allylated products were also obtained with the electrophiles Ph_2CO, Ph_2SiCl_2, Bu_2SnCl_2 and Ph_3SnCl, (entries 2–5). It is noteworthy that the NMR spectrum of the acid indicated barely detectable resonances in the aromatic region, implying that the undesired metalation of the allyl phenyl sulfide was not a competing reaction, at least to any appreciable extent. Analogous results were obtained with geranyl and neryl phenyl thioethers (entries 6 and 7). When the reductive lithiation of allyl phenyl thioether was performed in THF, the acid fraction after carboxylation was found to be a very complex mixture. Even when allyl phenyl sulfide was added to 2 equiv of preformed lithium naphthalene radical anion at −75 to −70 °C and the mixture stirred for 10 min at −80 °C followed by carboxylation, the acid fraction, in addition to 3-butenoic acid, contained acids derived from the lithiated sulfide, namely $CH_2=CHCH(SPh)COOH$, **1**, and $PhSCH=CHCH_2COOH$, **2**. In order to demonstrate the ready metalation of the allyl phenyl sulfide by allyllithium, we prepared allyllithium in diethyl ether and added it to a THF solution of allyl phenyl sulfide. Indeed, carboxylation of the mixture afforded an acid fraction, which was a mixture of the two expected carboxylic acids **1** and **2**, (Eq. 3).
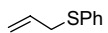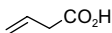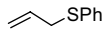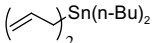

$$(3)$$
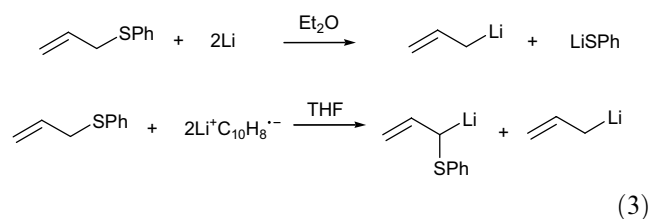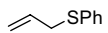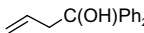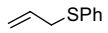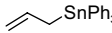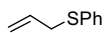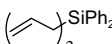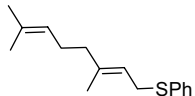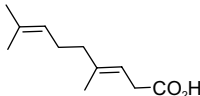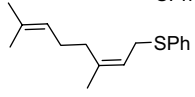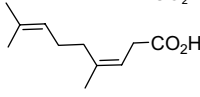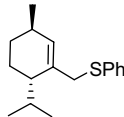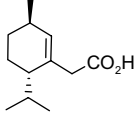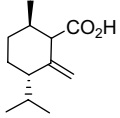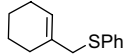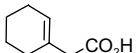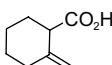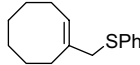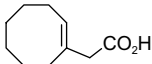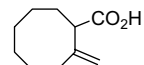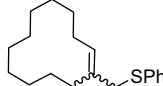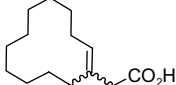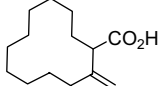
We also studied the reductive lithiation of carbocyclic allylic-type phenyl thioethers and the results are summarized in Table 1, (entries 8–11). The thioethers were synthesized by adding $PhSCH_2Li$ to (−)-menthone, C6, C8 and C12 cycloalkanones and subsequent dehydration of the resulting carbinols.[6] In Table 1, besides the yields of the carboxylic acids, the corresponding *endo/exo* ratios are also included, following the terminology of Ref. 6 (Eq. 4).

$$(4)$$
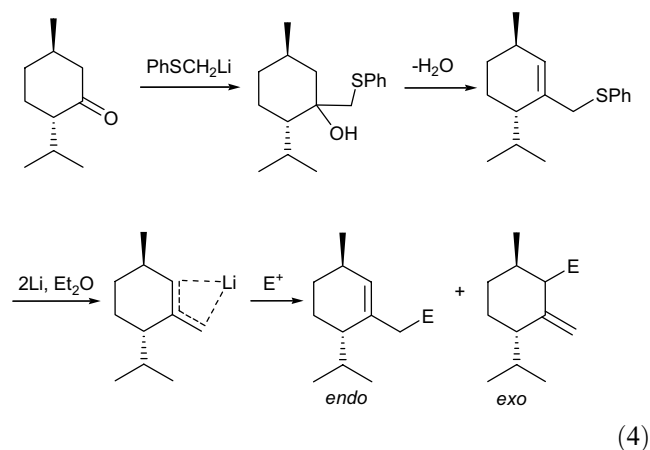
In these allylic-type organolithiums, two of the three carbon atoms that comprise the allylic system are incorporated into the carbocyclic ring, and therefore upon derivatization the electrophile has two options: either to form a bond with the exocyclic carbon giving the so-called *endo* olefinic product or with the appropriate ring carbon to afford the *exo* olefinic product. The olefinic proton(s) in the two isomers exhibit well-separated resonances and an estimate of the ratio of isomers was obtained by NMR analysis. More accurate *endo/exo* ratios were obtained by GC analysis on the mixture of the methyl esters.

It is also worth noting that it appears that, in the case of the reductive lithiation of cycloalkenylmethyl phenyl sulfides, the *endo/exo* ratio exhibits a rather marked solvent dependency. In THF, the *endo* isomer increases linearly and rapidly from C5 to C8 and then less steeply from C8 to C10, where it becomes almost the sole product.[6] If such a relationship were to hold also for diethyl ether, then in the case of C12 we ought to have obtained only the *endo* isomer. Instead, a 50–50 mixture of the two isomers was obtained consistently over several runs.

Table 1. Products from the reductive lithiation of allylic sulfides in diethyl ether after reaction with electrophiles

Entry	Thioether	Electrophile	Yield (%)[a]	Product(s)
1	=\SPh	CO_2	87	=\\CO_2H
2	=\SPh	n-Bu$_2$SnCl$_2$	82	(=\)$_2$Sn(n-Bu)$_2$
3	=\SPh	Ph$_2$CO	90	=\\C(OH)Ph$_2$
4	=\SPh	Ph$_3$SnCl	83	=\\SnPh$_3$
5	=\SPh	Ph$_2$SiCl$_2$	94	(=\)$_2$SiPh$_2$
6		CO_2	85	
7		CO_2	60	
8		CO_2	85 (95/5)	
9		CO_2	71 (79/21)	
10		CO_2	77 (85/15)	
11		CO_2	80 (50/50)	

[a] Figures in parentheses indicate the *endo/exo* ratio.

In conclusion, reductive lithiation of allyl phenyl sulfide in diethyl ether provides an efficient route to high yields of allyllithium. The reaction is devoid of complications arising from metalation of the thioether by the organolithium produced and, in addition, the procedure is less experimentally demanding than that involving reductive lithiation of allyl phenyl ether[12] and certainly less expensive than the one involving metal–metal interchange between allylstannanes and phenyllithium.[13]

General experimental procedure: Reductive lithiation reactions were carried out under an atmosphere of pure argon, using standard vacuum line and Schlenk techniques.

Allyl phenyl thioether was prepared by stirring at reflux a mixture of allyl chloride, thiophenol and potassium carbonate in ethanol for 1 h. Ethanol was removed under vacuum, water was added to dissolve salts and the product was taken up in CH_2Cl_2. The solution of the thioether was filtered through a short pad of silica gel covered with anhydrous sodium sulfate. Evaporation of the solvent yielded the thioether (99% pure by GC). Reported procedures were employed for the preparation

of geranyl phenyl thioether[14] and neryl phenyl thioether.[15]

The syntheses of 1-phenylthiomethyl-cyclohexene and -cyclooctene and their reductive lithiation in THF have been described previously[6] and (−)-1-phenylthio-methyl-*p*-menthene was prepared in an analogous fashion.

Typical reductive lithiation and carboxylation procedure: To 23 mL of anhydrous, argon-saturated diethyl ether were added 1.50 g, 10 mmol of allyl phenyl sulfide and 0.2 g, 29 mmol of lithium chips. The resulting mixture was stirred at ice-water bath temperature, 3–6 °C, for 2 h. Within a few minutes, the mixture turned yellow, then cloudy, milky and finally into a white thick slurry. The slurry was forced by a stream of argon through a cannula into a mixture of crushed solid carbon dioxide and anhydrous ether. Water (150 mL) was added to the carboxylation mixture at room temperature, followed by 1 mL of Me_2SO_4 and 2 mL of 50% aqueous NaOH. The resulting mixture was stirred for 2 h and then extracted with hexane (2×100 mL). The volume of the water layer was reduced by rotary evaporation almost to dryness, acidified with concentrated HCl and the resulting slurry extracted with CH_2Cl_2 (3×300 mL). The combined extracts were filtered through a pad of anhydrous sodium sulfate and the filtrate concentrated to a small volume by distilling the solvent through a 40 cm Vigreux column. Complete removal of the solvent was effected by rotary evaporation at room temperature. Yield 0.75 g, 87% (duplicate runs) of 3-butenoic acid.

For reactions with other electrophiles, the following typical procedure was followed: To allyllithium prepared from 10 mmol of allyl phenyl sulfide as described in the previous paragraph was added 1.05 mL, 5 mmol, of Ph_2SiCl_2 with ice bath cooling. After 0.5 h stirring, the reaction mixture was hydrolyzed, the solvent was removed by rotary evaporation and the product was taken up in CH_2Cl_2. The extract was washed three times with 10% aqueous NaOH solution, filtered through a pad of anhydrous sodium sulfate and the product freed from solvent by rotary evaporation. The residue was re-dissolved in hexane, and the cloudy solution was filtered. Hexane was removed under vacuum, leaving 1.25 g, 94%, of the title compound.

All products are known compounds and were identified by comparison with authentic NMR spectroscopic data.

References and notes

1. Streiff, S.; Robeiro, N.; Désaubry, L. D. *Chem. Commun.* **2004**, 346–347.
2. Screttas, C. G.; Micha-Screttas, M. *J. Org. Chem.* **1978**, *43*, 1064–1071.
3. Cohen, T.; Daniewski, W. M.; Weisenfeld, R. B. *Tetrahedron Lett.* **1978**, 4665–4668.
4. For reviews see: Clayden, J. In *Organolithiums: Selectivity for Synthesis, Tetrahedron Organic Chemistry Series*, 2002; Vol. 23, Chapter 4; Ramon, D. J.; Yus, M. *Eur. J. Org. Chem.* **2000**, 225–237; Yus, M.; Herrera, R. P.; Guijarro, A. *Chem. Eur. J.* **2002**, *8*, 2574–2584.
5. Screttas, C. G.; Eastham, J. F. *J. Am. Chem. Soc.* **1965**, *87*, 3276–3277.
6. Screttas, C. G.; Smonou, I. C. *J. Organomet. Chem.* **1988**, *342*, 143–152.
7. Fugita, T.; Suga, K.; Watanabe, S. *Synthesis* **1972**, 630.
8. Maercker, A.; Stumpe, R. W. *Tetrahedron Lett.* **1979**, 3843–3846; Maercker, A. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 972–989; Bartlett, P. D.; Tauber, C. W.; Weber, W. P. *J. Am. Chem. Soc.* **1969**, *91*, 6362–6366; Spialter, L.; Harris, C. W. *J. Org. Chem.* **1966**, *31*, 4263–4264; Screttas, C. G.; Micha-Screttas, M. *J. Org. Chem.* **1983**, *48*, 153–158.
9. Cohen, T.; Guo, B.-S. *Tetrahedron* **1986**, *42*, 2803–2808; Guo, B.-S.; Doubleday, W.; Cohen, T. *J. Am. Chem. Soc.* **1987**, *109*, 4710–4711; Kulkarni, V.; Cohen, T. *Tetrahedron* **1997**, *56*, 12089–12100.
10. Screttas, C. G.; Heropoulos, G. A.; Micha-Screttas, M.; Steele, B. R.; Catsoulacos, D. P. *Tetrahedron Lett.* **2003**, *44*, 5633–5635.
11. Cohen, T.; Kreethadumrongdat, T.; Liu, X.; Kulkarni, V. *J. Am. Chem. Soc.* **2001**, *123*, 3478–3483.
12. Eisch, J. J.; Jacobs, A. M. *J. Org. Chem.* **1963**, *28*, 2145–2146.
13. Yamamoto, Y.; Yatagai, H.; Maruyama, K. *J. Am. Chem. Soc.* **1981**, *103*, 1969–1975.
14. Fukuda, T.; Irie, R.; Katsuki, T. *Tetrahedron* **1999**, *55*, 649–664.
15. Morimoto, Y.; Iwai, T.; Kinoshita, T. *J. Am. Chem. Soc.* **1999**, *121*, 6792–6797.