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

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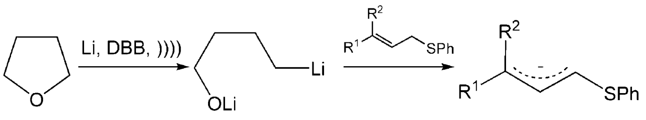
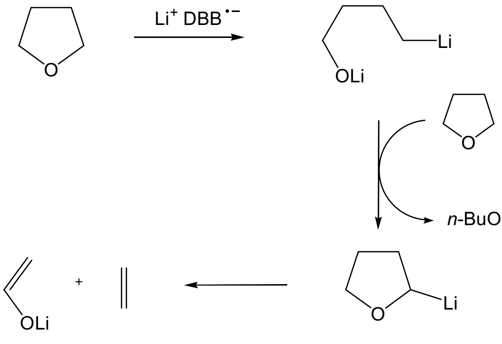
Abstract—Diethyl ether is a convenient solvent for the reductive lithiation of allylic phenyl thioethers without the serious complications, which occur when the reaction is carried out in tetrahydrofuran.

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)

Keywords: Reduction; Organolithium; Metalation; Regioselectivity.

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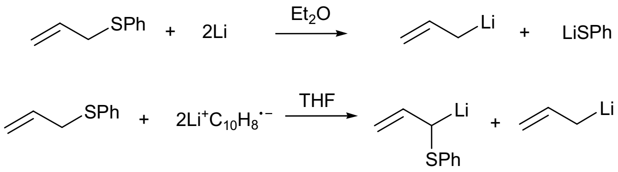
in THF, all the lithium was eventually consumed and that on hydrolysis acetaldehyde was produced along with *n*-butanol. These results also imply that $Li^{+}DBB^{\cdot -}$ decays by a 'silent' reductive ring opening of THF and formation of 4-lithioxybutyllithium, which subsequently decays by proton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

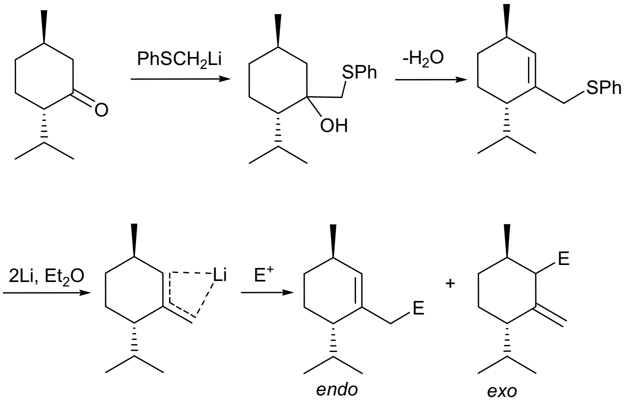
We have reported recently that alkyl phenyl thioethers may be reductively lithiated in diethyl ether,[10] thus extending the range of solvents which can be used for these reactions beyond THF and dimethyl ether.[11] However, even in diethyl ether, the *uncatalyzed* reductive lithiation of benzyl phenyl 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.