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Reductive lithiation of alkyl phenyl sulfides in diethyl ether. A ready access to α,α-dialkylbenzyllithiums

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Abstract—Diethyl ether is a convenient solvent for the conversion of benzylic phenyl sulfides to the corresponding organolithiums by an uncatalyzed reductive metalation, while catalysis by naphthalene is required to achieve the same reaction for alkyl phenyl sulfides. The addition of magnesium 2-ethoxyethoxide to solutions of unstable alkyllithiums prepared in this way provides storable reagents.

In a recent paper by Cohen et al.,[1] it was reported that the synthetically useful reaction of reductive lithiation[1,2] can be carried out in the absence of tetrahydrofuran (THF). The method involves generation of the radical anion in dimethyl ether, reductive lithiation of the sulfide in this medium and subsequent replacement of the medium by a more appropriate solvent, e.g. diethyl ether. Indeed, THF has conventionally been the solvent of choice for carrying out reductive lithiations either stoichiometrically[3–5] or by arene catalysis,[4] the reason for this preference being that, in THF, concentrated solutions of aromatic hydrocarbon radical anions can be generated.

In view of Cohen's report, the question arises as to whether the suitability of a solvent as a medium for carrying out reductive lithiations depends on its suitability or not for generating stable solutions of, for example, aromatic hydrocarbon radical anions. In this letter we wish to present experimental evidence, which demonstrates that reductive lithiation of alkyl phenyl sulfides can be conducted in diethyl ether, i.e. in a solvent unsuitable for generating radical anions, at least in synthetically useful concentrations.

Rapid magnetic stirring of a diethyl ether solution of α,α-dimethylbenzyl phenyl sulfide (cumyl phenyl sulfide) **1**, with lithium chips at 3–5°C for 2 h gave a 73% yield of α,α-dimethylbenzyllithium (cumyllithium) (see Table 1, entry 3). Given that α,α-dimethylbenzyl phenyl sulfide, when cleaved by lithium naphthalene radical anion or by lithium metal in THF, gives the dicumene almost exclusively,[6] the above result represents a remarkable solvent effect. Cohen has very reasonably attributed the failure of the reductive lithiation in THF solvent to the coupling between the cumyllithium and the cumyl phenyl sulfide,[7] an explanation that agrees with the statement that the phenylthio group behaves like a pseudohalogen.[4] In view of this interpretation, the successful conversion of **1** to cumyllithium in diethyl ether implies that, in this medium, the coupling reaction does not become very competitive with the lithiation reaction. Generally, sulfides of the type $ArC(R^1R^2)SPh$, where Ar = aryl, R^1,R^2 = aryl, alkyl or hydrogen as well as $ArCH{=}CHCH_2SPh$ may be reductively lithiated in diethyl ether (Eq. (1); see Table 1, entries 1–9).[8]

$$ArC(R^1R^2)SPh + 2Li \xrightarrow[\text{uncatalyzed}]{Et_2O} ArC(R^1R^2)Li + PhSLi \quad (1)$$

Alkyl phenyl sulfides, RSPh, however, failed to react with lithium chips in diethyl ether, at least at a synthetically convenient rate. This prompted us to try to carry out the reaction with naphthalene catalysis. When a 1 M solution of naphthalene in anhydrous argon-saturated diethyl ether was stirred with an excess of lithium chips, a red–purple coloration developed rapidly. Titra-

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Keywords: lithiation; reduction; thioethers; radical anion; magnesium alkoxide.

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Table 1. Reductive lithiation of alkylphenyl sulfides in diethyl ether[a]

Entry	Sulfide	RLi	Yield (%)
1	$PhCH(CH_3)SPh$	$PhCH(CH_3)Li$	68
2	$PhCH(CH_3)SPh$	$PhCH(CH_3)Li$	83[b]
3	$PhC(CH_3)_2SPh$	$PhC(CH_3)_2Li$	73
4	$PhC(i\text{-}Pr)(Me)SPh$[c]	$PhC(i\text{-}Pr)(Me)Li$	78[d]
5	$PhC(i\text{-}Pr)(Me)SPh$[c]	$PhC(i\text{-}Pr)(Me)Li$	90[b]
6	$Ph_2C(CH_3)SPh$	$Ph_2C(CH_3)Li$	78
7	$PhCH{=}CHCH_2SPh$	$PhCH{=}CHCH_2Li$	73
8	$c\text{-}(CH_2)_4C(Ph)SPh$[c]	$c\text{-}(CH_2)_4C(Ph)Li$	55
9	$c\text{-}(CH_2)_5C(Ph)SPh$	$c\text{-}(CH_2)_5C(Ph)Li$	60
10	$PhCH_2CH_2SPh$	$PhCH_2CH_2Li$	89[b]
11	$PhCH_2CH_2SPh$	$PhCH_2CH_2Li$	80[b,e,f]
12	$PhCH(CH_3)CH_2SPh$	$PhCH(CH_3)CH_2Li$	85[b]
13	Ph_2CHCH_2SPh	Ph_2CHCH_2Li	88[b]
14	$PhCH_2SPh$	$PhCH_2Li$	80[e]
15	$p\text{-}CH_3OC_6H_4CH_2SPh$	$p\text{-}CH_3OC_6H_4CH_2Li$	84[b,d,e,g]

[a] Unless otherwise noted all sulfides and carboxylic products are known compounds. Standard conditions: 5–10 mmol of sulfide, 40% excess of lithium metal chips, 15–30 mL of solvent, ice–water bath cooling, i.e. 3–8°C, reaction time 2 h. Yields are based on the amount of isolated carboxylic acids after carboxylation.[8]

[b] In the presence of 25% naphthalene as a catalyst, stoichiometric amount of lithium chips.

[c] New compounds, see Ref. 13.

[d] Reaction time: 3 h.

[e] In the presence of 1 mol equiv. of magnesium 2-ethoxyethoxide.

[f] Carboxylation after standing for 8 days at room temperature.

[g] Carboxylation after standing for 2.5 days at room temperature.

tion of an aliquot of such a solution indicated only a minute (0.05 M) total alkalinity, *regardless of the duration of stirring*. Despite the very low concentration of the lithium containing species, namely the dilithium naphthalene dianion,[10] it is effective in catalyzing the conversion of alkyl phenyl sulfides to the corresponding alkyllithiums (Eq. (2); Table 1, entries 10–13). The greater ease of cleavability of the benzylic type sulfides as compared to that of the alkyl phenyl sulfides, can be reasonably attributed to the relative thermochemical stabilities of the radicals $Ar(R)_2C^{\bullet}$ and $R^{\bullet}$ which are most probably involved in the reductive process,[11] these stabilities being a reflection of the respective C–SPh bond strengths.

$$\mathrm{RSPh} + 2\mathrm{Li} \xrightarrow[\substack{\text{catalytic naphthalene} \\ \mathrm{R = alkyl}}]{\mathrm{Et_2O}} \mathrm{RLi} + \mathrm{PhSLi} \qquad (2)$$

The generation of organolithium reagents in diethyl ether may provide a number of additional advantages over THF. Alkyllithiums are more stable in diethyl ether than in THF, thus permitting higher reaction temperatures for their preparation. Also, the propensity of ketones to enolize is diminished on going from THF to Et_2O, and thus higher yields of addition products with organolithium reagents in diethyl ether may be realized. In addition, in diethyl ether styrenes undergo efficient addition reactions with primary, secondary and tertiary organolithium reagents to produce α,α-substituted benzyllithiums, whereas in THF styrenes undergo anionic oligo- or polymerization.[1,12]

It is of importance to note that, under naphthalene catalysis in the presence of an excess of lithium, the reaction leads to a mixture containing, besides the organolithium derived from the sulfide, lithiated species derived from naphthalene as well, the amount of which depends on the quantity of naphthalene used. This is somewhat puzzling since naphthalene and lithium in diethyl ether and in the absence of sulfide, as has already been mentioned, react only to a very small extent. It appears, therefore, that some sort of synergism is operable in the system sulfide, lithium and naphthalene. The contamination of the desired organolithium product by lithiated naphthalenes can be avoided either by keeping the amount of catalytic naphthalene as low as possible or by employing a stoichiometric quantity of lithium. In the latter case, the amount of naphthalene may be increased without serious problems.

Solutions of the organolithiums prepared in diethyl ether should be used immediately after their preparation. In order to make them storable, we studied briefly their possible stabilization by adding magnesium 2-ethoxyethoxide.[14] In this way, carrying out the reductive lithiation of *p*-methoxbenzyl phenyl sulfide at room temperature under naphthalene catalysis and in the presence of an equimolar amount of magnesium 2-ethoxyethoxide, an 84% yield of *p*-methoxyphenylacetic acid was obtained by carboxylating the reaction mixture which had subsequently been left to stand for 2.5 days. Similarly, the sulfide $PhCH_2CH_2SPh$ gave an 80% yield of 3-phenylpropionic acid after 8 days at room temperature. In this context, the stabilization of an otherwise unstable carbanion such as *p*-methoxybenzyl is rather remarkable. Cumyl phenyl sulfide, on the other hand, under the same conditions gave ultimately bicumyl, although in the early stages of the reaction the mixture was reddish colored. Even when magnesium alkoxide is added to preformed cumyllithium the latter is destroyed within about 1 h at room temperature as deduced from the discharge of the color and the failure to produce any carboxylic acid upon carboxylation. It is of interest to note that in both cases the decay of cumyllithium in the presence of magnesium alkoxide leads to the formation of bicumyl. The latter compound is obviously produced by homolysis of a weak carbon–metal bond, probably of $PhC(CH_3)_2$–$MgOCH_2CH_2OEt$. Cumyllithium also reacts with mercuric chloride and again affords bicumyl, as should be expected. It should also be mentioned that reductive lithiation of benzyl phenyl sulfide in diethyl ether should be conducted in the presence of 1 equiv. of magnesium 2-ethoxyethoxide (Table 1, entry 14). Otherwise, the final product is lithiated benzyl phenyl sulfide (Eq. (3)). The same holds for *p*-methoxbenzyl phenyl sulfide (Table 1, entry 15).

$$\begin{aligned} &\mathrm{PhCH_2SPh} + 2\mathrm{Li} \longrightarrow \mathrm{PhCH_2Li} + \mathrm{PhSLi} \\ &\mathrm{PhCH_2Li} + \mathrm{PhCH_2SPh} \longrightarrow \mathrm{PhCH(SPh)Li} + \mathrm{PhCH_3} \end{aligned} \qquad (3)$$

In summary, diethyl ether is found to be a convenient solvent for the conversion of benzylic type phenyl sulfides to the corresponding organolithiums by an uncatalyzed reductive metalation. Alkyl phenyl sulfides, however, require catalysis by naphthalene in order to undergo reductive lithiation in the same medium. Unstable alkyllithiums prepared in this way can be stabilized by the addition of magnesium 2-ethoxyethoxide and thus be used as storable reagents.

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   For the reactions in which $Mg(OCH_2CH_2OEt)_2$ was also used, the volume of water added after the carboxylation step was increased to 250 mL and then subsequently reduced as above in order to ensure complete removal of the 2-ethoxyethanol formed by hydrolysis of the alkoxide.
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