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LITHIO ALKYL PHENYL THIOETHERS AS USEFUL REAGENTS FOR CARBON-CARBON BOND FORMATION

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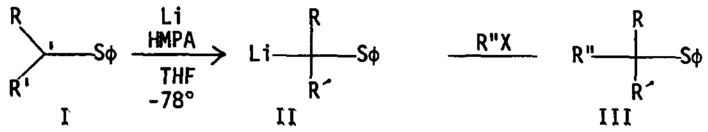
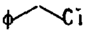
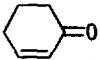
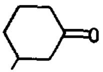
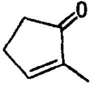
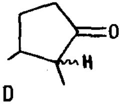
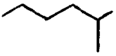
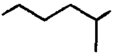
The synthetic versatility of organosulfur compounds has led to extensive investigations into the chemistry of mercaptals,[1] allylic sulfides,[2] sulfoxides,[3] sulfones,[4] α-sulphenyl ketones and esters,[5] thioesters,[6] vinylogous thioesters[7] and analogous chemical species. A significant portion of these studies has entailed various metallated forms of these organosulfur compounds, but the metal salts of simple alkyl aryl sulfides have received only limited attention. Phenylthiomethyllithium[8] and methylthiomethyllithium[9] have been generated from thioanisole and dimethyl sulfide using n-butyllithium in the presence of either diazabicyclo-[2.2.2]octane (DABCO) or tetramethylethylene diamine (TMEDA). However, attempts to generate the α-metallated species of the higher homologs of alkyl aryl sulfides using the above conditions have led to metallation of sites other than adjacent to sulfur (e.g. aromatic ring positions) and elimination products.[10] More recently, Krief has successfully generated lithioalkyl phenyl sulfides by the n-butyllithium induced cleavage of alkyl phenylselenyl phenyl sulfides.[11] Reported herein is a simple method for generation of lithioalkyl phenyl sulfides (II) by direct proton abstraction and the reactions of these systems.

The addition of tert-butyllithium (1.2 eq) to a THF solution of alkyl aryl sulfide (I) and hexamethylphosphoramide (HMPA; 2.5 eq) at -78°C resulted in the metallation of I. Quenching of this characteristically orange solution (after 2-3 hr at -78°) with D_2O afforded products deuterated at the 1-alkyl position (∿100% deuterium incorporation).[12] When the lithium salt of isobutylphenyl sulfide (IIb), formed as above was warmed to 0°C for 3 hr prior to quenching with D_2O, deuteration at the position adjacent to sulfur was still observed (> 85%) with some deuterium being incorporated at other sites (∿100% deuterium incorporation).[12] As expected, treatment of thioanisole using the above conditions (t-butyllithium and HMPA) followed by D_2O quenching afforded only methyl deuteration (∿100% deuterium incorporation);[12] results analogous to those of Corey (ϕSCH_3, n-butyllithium and DABCO).[8] Reaction of isobutylphenyl sulfide (Ib) with n-butyllithium using the procedure of Corey (0°C, DABCO)[8] or the procedure of Peterson (0°C, TMEDA)[9] followed by quenching with D_2O led to products with considerable deuteration of the aromatic ring (70-80%) and only moderate amounts of deuteration at the 1-alkyl position (15-20%), as well as some thiophenol, which apparently is formed by elimination[8,10] (90-95% deuterium incorporation[12]).

Table I



	Sulfide (I)		Alkylating Agent	Product(III)	Yield[13]
	R	R'			
Ia	H	H	D_2O	$D\text{-}CH_2S\phi$	∿100%
Ib	H	i-propyl	D_2O	R"= D	∿100%
Ib	H	i-propyl	Me_3SiCl	R"= $SiMe_3$	86%
Ib	H	i-propyl	EtI	R"=Et	74%
Ib	H	i-propyl	EtBr	R"=Et	79%
Ib	H	i-propyl		R"= 	82%
Ib	H	i-propyl	ϕCHO	$R''=\overset{OH}{C}H\phi$	92%
Ib	H	i-propyl	ϕCO_2Me	$R''=\overset{O}{\overset{\|}{C}}\phi$	46%
Ib	H	i-propyl	ϕCN	$R''=\overset{O}{\overset{\|}{C}}\phi$	61%
Ib	H	i-propyl		stilbene	78%
Ib	H	i-propyl		R"= 	56%
Ib	H	i-propyl		R"= 	57%
Ic	H	MeO	D_2O	R"= D	∿100%
Ic	H	MeO	Me_3SiCl	R"= $SiMe_3$	92%

Further investigation of the chemistry of these lithioalkyl phenyl sulfides (II) has resulted in the formation of a wide range of synthetic intermediates (see Table I) from their reaction with various electrophiles. For example, addition of ethyl bromide or ethyl iodide (1.2 eq.) to the lithium salt of isobutylphenyl sulfide (IIb) at -78°C with subsequent warming to room temperature, dilution with water and extraction with ether afforded phenyl 2-methyl-1-ethylpropyl sulfide contaminated only by small amounts of unreacted starting material. Under the same conditions, IIb and allyl bromide (1.2 eq) gave phenyl 1-isopropyl-3-butenyl sulfide in good yield. In contrast to the above alkylations, only stilbene and starting sulfide were isolated when benzyl chloride was added to IIb at -78°C, a result previously observed with other highly basic organometallic reagents.[3] Quenching of IIb with trimethylchlorosilane afforded phenyl 2-methyl-1-trimethylsilylpropyl sulfide. Phenylthiotrimethylsilylmethane has been previously employed by Peterson and others for the formation of terminal vinyl sulfides[14] thus alkylation of lithioalkyl phenylsulfides (II) provides a possible extension of Peterson's procedure to more complex vinyl sulfides. In addition to these alkylations, condensation of IIb with benzonitrile or methyl benzoate afforded 2-methyl-1-phenylthiopropylphenone with the yields of these products being indicative of some proton exchange between II and products. Such α-phenylthioketones have been prepared by alkylation of enolates with phenyldisulfide.[5]

In contrast to some other sulfur stabilized metal salts which add in a 1,2 fashion to enones,[1,15] the reaction of cyclohexenone with IIb afforded 3-(2-methyl-1-phenylthiopropyl)-cyclohexanone (56%), i.e., the product of 1,4-addition. The conjugate or 1,4-addition was somewhat surprising to us but was also observed with 2-methyl-2-cyclopentanone (Table I) and may be directly attributable to solvation effects of the required HMPA.[16]

These results demonstrate the utility of α-lithioalkyl phenyl sulfides. Combination of these results with the array of organosulfur chemistry present in the literature generates some interesting synthetic possibilities that are currently being pursued in these laboratories.

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