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Direct Deprotonation of Aliphatic Sulfides

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Abstract: Alkylmethyl sulfides are regioselectively deprotonated by *n*-butyllithium and potassium *tert*-butoxide at the methyl group in good yields. Thiolane and thiane are deprotonated under the same conditions at the α-position in good yield. © 1997 Elsevier Science Ltd.

α-Metalated sulfides are useful synthetic intermediates.[1,2] Deprotonation of thioanisole with *n*-butyllithium and DABCO gives phenylthiomethyllithium,[3] dimethylsulfide with *n*-butyllithium and TMEDA affords methylthiomethyllithium,[4] and phenyl cyclopropyl sulfide with *n*-butyllithium provides 1-lithiocyclopropylphenyl sulfide[5] in excellent yields. However, such direct deprotonation is limited in scope[4,6,7] although deprotonation of sulfides with neighboring, metal-complexing oxygen[8,9] or carboxamide[10] moieties have also been shown to be synthetically valuable. Deprotonation of thioanisole, isobutyl phenyl sulfide, and (5-methoxy-2-methylpentyl) phenyl sulfide with *tert*-butyllithium and HMPA has also been reported[11] to give the corresponding lithio alkyl phenyl sulfides but the generality of this method has not been shown. Consequently, other methods have been used to prepare phenylthiocarbanions, or their synthetic equivalents, such as lithium selenium exchange of α-selenosulfides,[9,12-15] reductive metalation,[9,15,16] fluoride ion desilylation of α-silylsulfides,[17,18] and intramolecular carbolithiation of vinylsulfides.[19] This paper reports the significant extension of the scope of preparing α-metalated sulfides by direct deprotonation using *n*-butyllithium and potassium *tert*-butoxide.[20-25]

Reaction of alkyl methyl sulfides **1a-c** with *n*-butyllithium and freshly sublimed

$$RSCH_2R^1 \longrightarrow RSCH(R^1)Sn(c\text{-}C_6H_{11})_3$$

1a, $R=CH_3$	**2a**, $R=CH_3$, $R^1=H$
b, $R=CH_3(CH_2)_9$	**b**, $R=CH_3(CH_2)_9$, $R^1=H$
c, $R=(CH_3)_2CHCH_2$	**c**, $R=(CH_3)_2CHCH_2$, $R^1=H$
d, $R=CH_3CH_2$, $R^1=CH_3$	**d**, $R=CH_3CH_2$, $R^1=CH_3$

potassium *tert*-butoxide in anhydrous THF at -40° followed by quenching with tri(cyclohexyl) stannyl chloride gave **2a-c** in good to excellent isolated yields as shown in Table 1. Not only was *n*-decyl methylsulfide **1b** selectively deprotonated in excellent yield in contrast to the results with *n*-butyllithium and TMEDA,[4] but the methyl group was also selectively deprotonated in isobutyl methyl sulfide, **1c**, as well. Reaction of the product obtained by deprotonation of dimethyl sulfide with benzaldehyde also helped further establish its structure. Known[26] adduct **3a**

$\mathrm{RSCH(R^1)CH(OH)Ph}$

3a, $\mathrm{R{=}CH_3, R^1{=}H}$
b, $\mathrm{R{=}CH_3CH_2, R^1{=}CH_3}$

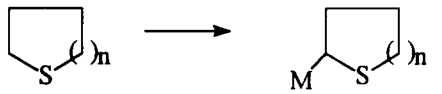
$\mathrm{CH_3CH_2SCH(CH_3)COPh}$

4

was obtained quantitatively and the melting point of its methiodide matched the reported melting point.

To ascertain whether deprotonation of a primary α-hydrogen could be achieved, diethyl sulfide **1d** was studied. The best conditions found for this deprotonation were treatment with *n*-butyllithium and potassium *tert*-butoxide in THF at -78°C for 20 min followed by reaction with tri(cyclohexyl) stannyl chloride or benzaldehyde to produce **2d** and **3b**, respectively in poor yield (see Table 1). Known[26] **3b** is produced as a mixture of diasteromers that was converted to **4**, as reported, for identification. Attempts to deprotonate diethyl sulfide at higher temperatures resulted in even poorer yields of product presumably due to decomposition of the α-metalated sulfide.

Despite the poor yields for deprotonation of diethyl sulfide, excellent yields were obtained for deprotonation of thiolane **5a** and thiane **5b** with *n*-BuLi/KO*t*-Bu in THF at -40° for 1-2h and subsequent trapping in good to excellent yields as shown in Table 1. The structure of **6a** was established by ^{1}H NMR, ^{13}C NMR, IR and mass spectroscopic analysis and elemental analysis as was the case for the other new compounds but, in addition, by its identity with material prepared by the following alternate route. Treatment of thiolane **5a** with N-chlorosuccinimide in benzene afforded the corresponding α-chlorosulfide. Reaction of this material with $\mathrm{Me_3SnLi}$ in THF produced **6a** in an overall yield of 17%



5a, n=1
b, n=2

6a, n=1, $\mathrm{M{=}SnMe_3}$
b, n=1, $\mathrm{M{=}Sn(\mathit{c}\text{-}C_6H_{11})_3}$
c, n=1, $\mathrm{M{=}Si(\mathit{i}\text{-}Pr)_3}$
d, n=2, $\mathrm{M{=}SnMe_3}$
e, n=2, $\mathrm{M{=}Sn(\mathit{c}\text{-}C_6H_{11})_3}$
f, n=2, $\mathrm{M{=}Si(\mathit{i}\text{-}Pr)_3}$

$\mathrm{CH_2{=}CHSR}$

7a, $\mathrm{R{=}Si(\mathit{i}\text{-}Pr)_3}$
b, $\mathrm{R{=}Sn(\mathit{c}\text{-}C_6H_{11})_3}$

Some insight into the stability of the carbanion formed by deprotonation of thiolane **5a** by *n*-BuLi/KO*t*-Bu was obtained when the deprotonation was carried out at -30° for 1.5h followed by silylation with tri(isopropyl) silyl chloride. In addition to **6c**, silylated vinyl sulfide **7a** was isolated in 13% yield. Note the small difference in temperature between that at which deprotonation occurs at a reasonable rate and that at which the onset of decomposition of the α-metalated thiolane occurs. Treatment of thiolane **5a** with *n*-BuLi/KO*t*-Bu in THF at 5°C for 1h resulted in complete decomposition of the carbanion and addition of tri(cyclohexyl)stannyl chloride gave **7b** in quantitative yield. The decomposition pathway followed by α-metalated thiolane appears to be analogous to that followed by α-lithio THF.[27]

Finally attempts to deprotonate di-isopropyl sulfide and trap the corresponding carbanion were unsuccessful.

Table 1. Direct Deprotonation[a] of Alkylsulfides Followed by Reaction with an Electrophile

Sulfide	Electrophile	Product	Isolated Yield (%)
1a[b]	$(c\text{-}C_6H_{11})_3SnCl$	**2a**	97
1b[b]	$(c\text{-}C_6H_{11})_3SnCl$	**2b**	86
1c[b]	$(c\text{-}C_6H_{11})_3SnCl$	**2c**	58
1a[b]	PhCHO	**3a**	99
1d[c]	$(c\text{-}C_6H_{11})_3SnCl$	**2d**	23
1d[c]	PhCHO	**3b**	19
5a[b]	Me_3SnCl	**6a**	90
5a[b]	$(c\text{-}C_6H_{11})_3SnCl$	**6b**	70
5a[b]	$(i\text{-}Pr)_3SiCl$	**6c**	62
5b[b]	Me_3SnCl	**6d**	70
5b[b]	$(c\text{-}C_6H_{11})_3SnCl$	**6e**	55
5b[b]	$(i\text{-}Pr)_3SiCl$	**6f**	85

[a] Deprotonation with *n*-butyllithium and potassium *tert*-butoxide in anhydrous THF

[b] Deprotonation conditions: -40°C, 1-2h

[c] Deprotonation conditions: -78°C, 20 min

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