ORIGINAL REACTIONS OF α,α-DITHIO ARYL ALKANES WITH BUTYLLITHIUMS

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Abstract: Thioacetals derived from aromatic ketones react with butyllithiums already at -78 °C and produce via a reductive process the corresponding α -thiobenzyllithiums in high yields. The same reaction also takes place selectively, under suitable conditions, with the thioacetals derived from benzaldehyde on which a competing metallation reaction is also possible. These observations clearly show that the thioacetal functionality is not a suitable protecting group against alkyllithiums for aromatic carbonyl compounds.

Since the fundamental work of Corey and Seebach ¹ it is well established ² that n-butyllithium in THF reacts as a base with 1,1-dithioalkanes to produce 1,1-dithioalkyllithiums in high yields via an isohypsic ³ process. This reaction proved to be quite general allowing the high yield synthesis of a large variety of these species which proved particularly useful in synthesis as acyl anion equivalents.^{1,2} The same alkyllithium reacts however as a nucleophile with the analogous α, α -diseleno-⁴ and α, α -ditelluro-^{4f,5} alkanes which instead lead to the corresponding α -seleno- and α -telluro-alkyllithiums via a reduction reaction. This transformation is also general and for example 1,1-diselenotoluene, which is expected to be one of the most easily metallated member of this series, is also cleanly reduced ⁶ by n-butyllithium to the corresponding α -selenobenzyllithium.

We now report that thioacetals derived from aromatic ketones 1^7 which are unable to be metallated at the same place for structural reasons, behave as their seleno analogues towards butyllithiums and produce α -thiobenzyllithiums 2^8 in reasonably good yields. We have also found that even some thioacetals, derived from aromatic aldehydes 1', which are usually metallated,⁹ can be reduced by butyllithiums under suitable conditions.

Scheme 1

	S Ph—C I M	R ₁ :SR ₂ le	RLi, S T (°C)	olvent , t (h)	$\begin{bmatrix} SR' \\ Ph-C-Li \\ Me \end{bmatrix} \xrightarrow{E50^{\circ}C, 0.2 h} Ph-C-E \\ \downarrow \\ Me \end{bmatrix} Me$						
	1				$2 \qquad E = MeOH \qquad 3 : E = H \\ E' = PhCH=O \qquad 4 : E = PhCHOH$						
entries	R ₁	R ₂	1	R	R'	Solvent	T (°C)	t (h)	Yield in 3	ratio* 3 / 1	Yield in 4
a	Ph	Ph	la	n-Bu	Ph	THF	- 78	0.50	81	100/0	95
b	Me	Me	1b	n-Bu	Me	THF	- 78	0.50		1 0/9 0	
с	Me	Ме	1 b	n-Bu	Me	THF	- 50	0.50		90/10	85
d	-CH ₂ — C	CH2-	1c	n,s,t-Bu	$(CH_2)_2SR$	THF	- 78	0.50	>81	100/0	75
e	-CH ₂ (0	CH2)2-	id	n-Bu	(CH ₂) ₂ SR	THF	- 78	0.50	80	0/100	
f	$-CH_2 - (0)$	CH2)2-	1đ	n-Bu	(CH ₂) ₃ SR	THF	- 50	0.50		10/90	
g	$-CH_2 - (0)$	CH2)2-	1d	n-Bu	(CH ₂) ₃ SR	THF	- 30	0.75		97/03	
h	-CH ₂ (0	CH2)2-	ld	s, t-Bu	(CH ₂) ₃ SR	THF	- 50	0.20	>82	100/0	80
i	-CH ₂ — C	CH2-	lc	s-Bu	(CH ₂) ₂ SR	Et ₂ O	- 78	0.25		90/10	
j	-CH ₂ — C	'H2-	l¢	s-Bu	(CH ₂) ₃ SR	Pentane	- 78	0.25		10/90	
k	$-CH_2 - (0)$	CH2)2-	ld	s-Bu	(CH ₂) ₃ SR	Et ₂ O	- 50	0.25		86/14	
1	-CH ₂ —(CH2)2-	1d	s-Bu	(CH ₂) ₃ SR	Pentane	0	0.25	•-	02/98	

* These ratios have been obtained by G.C. analysis

In a preliminary study we have reacted 1,1-bis(phenylthio)-1-phenyl ethane 1a, its bis(methylthio) analogue 1b as well as 2-methyl-2-phenyl-1,3-dithiolane 1c and -dithiane 1d with butyllithiums in THF, ether or pentane at different temperatures. We have then quenched the medium with methanol at the same temperatures and have determined the ratio of the unreacted thioacetal 1 and of the sulfide 3 resulting from the S-C bond cleavage. The results are summarized in the scheme 1. As general trends n-butyllithium in THF is efficient enough for the S/Li exchange from those thioacetals derived from acetophenone. The reaction takes place very rapidly (< 0.5h) and almost quantitatively at -78°C for the *bis(phenylthio)* 1a and dithiolane 1b derivatives which proved to be the most reactive one's (scheme 1 compare entries a, d to entries b, e). The bis(methylthio) analogue 1b as well as the 1,3-dithiane derivative 1d are not however cleaved under these conditions and require the use of a higher temperature (-50°C or -30°C) to react (scheme 1 compare entries c, g to entries b, e). Secondary and tertiary butyllithiums are more reactive than n-butyllithium whether THF or ether is used as the solvent (scheme 1 compare entries h to entries f). Finally the S/Li exchange proved to be more effective in THF than in ether and is much more difficult in pentane (scheme 1 compare entries h, k and l). These features are similar to those we have reported for the reaction of butyllithiums with selenoacetals.^{4,6} The latter derivatives are nevertheless more reactive than their thio analogues.

Thioacetals derived from benzaldehyde were more intriguing since metallation, leading to acyl anion equivalents, is the usually observed reaction.^{1,2,9} We indeed found that this is mainly the case with 2-phenyl-1,3-dithiane **1'd**. Bis(phenylthio) phenyl methane **1'a** however can be selectively metallated (H/Li exchange) or cleaved (S/Li exchange) depending upon the nature of butyllithium and solvent used. n-Butyllithium in THF proved to be the most efficient for the former purpose whereas s- or t-butyllithium in ether were found to be the most valuable combinations for the latter transformation (scheme 2). We have also surprisingly observed that n-butyllithium in THF possesses a higher propensity to react as a base towards bis(phenylthio) phenyl methane **1'a** than s- or t-butyllithium in the same solvent (scheme 2), although it is usually admitted that the most hindered reagent is the one which possesses the highest propensity to act as a base. Unfortunately we have not found conditions which allow ¹⁰ a clean reaction on 2-phenyl-1,3-dithiolane **1'c**.

Ph—	SPh C—SPh · H	(i) RLi, Solvent, -50°C, 0.5h (ii) D ₂ O	SPh ▶ Ph—C—D + H	SPh Ph-C-SPh D
	1'a		3'a'	1'a'
entries	R	Solvent	3'a' (%)	1'a'(%)
a	n-Bu	THF	08	92
b	s-Bu	THF	47	51
с	t-Bu	THF	67	28
đ	s-Bu	Et ₂ O	73	05
e	t-Bu	Et ₂ O	78	05

Scheme 2

The α -thiobenzyllithiums prepared above have been also successfully reacted with benzaldehyde and in one case with 5-bromo-1-pentene to produce the corresponding β -hydroxyalkyl sulfides 4 (scheme 1) or the ω -alkenyl sulfide 8 respectively (scheme 3) in good yields. Bis(phenylthio) phenyl methyllithium also leads to the corresponding alcohol on reaction with benzaldehyde but the yield is quite low probably due to the tendency of the corresponding alcoholate to undergo a reverse reaction ¹¹ giving back benzaldehyde and bis(phenylthio) phenyl methyllithium. In the course of this work we have reacted, at 0°C, the 6-phenyl-6,6-bis(methylthio)-1-hexene ¹² 1"b shown in the scheme 4 with n-butyllithium in THF. We have observed that the resulting 6-phenyl-6-methylthio-1-heptene-6-yllithium 2" is stable at 0°C or even at 20°C and surprisingly does not exhibit the high propensity of its methylseleno analogue to produce 1-phenyl bicyclo[3.1.0]hexane 5.¹³ That 2" is still present after this treatment (20°C, 0.5h) has been unambiguously proved by its efficient trapping with benzaldehyde (scheme 4). We also found (scheme 3) that under particularly drastic conditions tertio-butyllithium (2 equiv., THF, -30°C, 0.5h) ¹⁴ is able to cleave the C-S bond of 6-phenyl-6-phenylthio-1-heptene 8 producing, after quenching with methanol, 1,2-dimethyl-1-phenyl cyclopentane 9 in very good yield but with a quite modest stereoselectivity (9E/9Z: 85/15).¹⁵



Scheme 3

(i) n-BuLi, THF, -50°C, 0.5h (ii) 5-bromo-1-pentene, -50°C, 0.5h then 25°C, 0.5h (iii) n-BuLi, THF, -30°C, 0.5h, (iv) MeOH, -30°C, (9E/9Z: 85/15).

The α -thioalkyllithiums we have prepared by the cleavage of one of the C-S bond of thioacetals can be also obtained by metallation of the corresponding benzyl sulfides.⁹ The set of reactions presented in the scheme 3 nevertheless offers the advantage to allow the formal geminal di-alkylation of the carbonyl group of aromatic ketones a process we already described using the corresponding seleno analogues.^{15a,b} Furthermore the results reported here clearly show that the thioacetal moiety is not a suitable protecting group for the carbonyl group of aromatic aldehydes and ketones.

The cleavage of the C-S bond by alkyllithiums ¹⁶ is not as general as that of the C-Se ^{4e,g} or the C-Te bonds.^{4e,5,17} Nevertheless some precedent which involve compounds (i) in which the sulfur atom is part of a strained cycle ¹⁸ or (ii) which are able to produce after cleavage a novel organolithium species possessing particularly well stabilized carbanionic centers ¹⁹ have been reported in the literature.²⁰



(i) n-BuLi, THF, -50°C, 0.5h (ii) 5-bromo-1-pentene, -50°C, 0.5h then 25° C, 0.5h (iii) n-BuLi, THF, 0°C, 1.5h, (iv) MeOH or PhCH=0, 0°C, 0.2h then 25° C, 0.2h.

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