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THE REDUCTIVE LITHIATION OF THIOACETALS, α,α-BIS(TRIMETHYLSILYL)-ALKYL SULFIDES, AND 2-ALKYL-2-ETHYLTHIOALKANENITRILES USING TRIBUTYLSTANNYLLITHIUM

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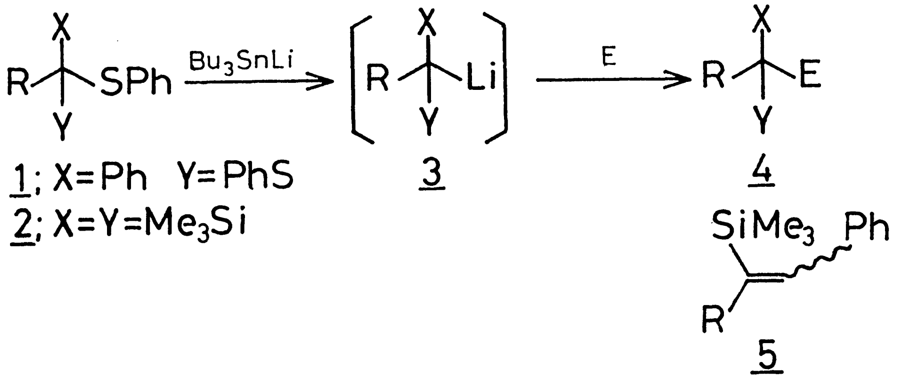
The reaction of thioacetals of phenyl ketones, α,α-bis(trimethylsilyl)alkyl sulfides, and 2-alkyl-2-ethylthioalkanenitriles with tributylstannyllithium gave the corresponding α-anions of sulfides, α,α-bis(trimethylsilyl)alkane, and nitriles, respectively.

Desulfurization of organosulfur compound has been investigated as an indispensable process in the synthesis utilizing α-thio carbanions and various reagents were developed for this purpose.

Concerning the preparation of carbanions by the reductive removal of alkylthio group (reductive metallation), Screttas reported that the simple sulfides were reduced to the corresponding alkyllithiums with lithium dispersion or lithium naphthalenide.[1)] The latter reagent was also employed for the reductive lithiation of thioacetals[2)] and α-trimethylsilyl sulfides.[3)]

We have investigated a facile method for the reductive removal of alkylthio group in conjunction with our study on the synthesis of organosulfur compounds. Therein, we report a new method for the reductive lithiation of some organosulfur compounds utilizing tributylstannyllithium and the application of this method to the synthesis of 2,2-disubstituted alkanenitriles.

When the thioacetals of phenyl ketones (1) were treated with tributylstannyllithium in THF at 0 °C, the corresponding sulfides were produced in good yields. It was assumed that the reduction proceeded via the α-thio carbanion intermediate (3). In fact, the treatment of the reaction mixture with aldehydes or alkyl halides gave β-hydroxy sulfides or alkylated sulfides (4) in good yields.



(1)

Further it was found that the reduction of α,α-bis(trimethylsilyl)alkyl phenyl sulfides (2) followed by the treatment with benzaldehyde afforded alkenylsilanes (5) (Eq. 1, Table 1).

Table 1. The reductive lithiation of thioacetals and α,α-bis(trimethylsilyl)alkyl phenyl sulfides a)

R	X	Y	Reductive lithiation			E	Yield 4)
			Solvent	Temp °C	Time min		%
CH_3	Ph	PhS	b)	0	15	PhCHO	86
CH_3	Ph	PhS	b)	0	15	CH_3CH_2CHO	81
CH_3	Ph	PhS	b)	0	15	CH_3I	94
CH_3	Ph	PhS	b)	0	15	$CH_3(CH_2)_7I$	79 d)
CH_3	Ph	PhS	b)	0	15	$PhCH_2Br$	78
CH_3CH_2	Ph	PhS	b)	0	15	$(CH_3)_2CHCH_2CHO$	74
CH_3CH_2	Ph	PhS	b)	0	15	CH_3I	76
$CH_3(CH_2)_7$	Ph	PhS	b)	0	15	$(CH_3)_2CHCH_2CHO$	78
$CH_3(CH_2)_3$	$(CH_3)_3Si$	$(CH_3)_3Si$	c)	-78	120	PhCHO	74,(62 e))
$PhCH_2$	$(CH_3)_3Si$	$(CH_3)_3Si$	c)	-78	30	PhCHO	76

a) All the reactions were carried out by a similar procedure to that described for the reaction of 2-ethylthioalkanenitriles.

b) 3 ml/mmol of THF was used.

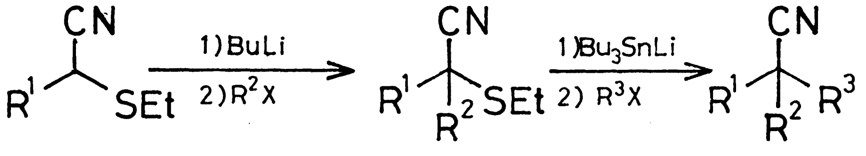
c) 4 ml/mmol of THF and 2 ml/mmol of HMPA were used.

d) 1 ml/mmol of HMPA was added with octyl iodide.

e) The reported yield of the alkenylsilane obtained by the reaction using lithium naphthalenide.3a)

Tributylstannyllithium in THF is thermally stable and can be stored for several months. On the other hand, lithium naphthalenide must be prepared just before use and handled at low temperature. Accordingly the tributylstannyllithium reduction of organosulfur compounds has an advantage in that the reaction procedure is simple.

It is well known that the alkylation of nitriles is complicated by multiple alkylation owing to formation of the α-anion of the initially alkylated product. Therefore we attempted to apply the present reductive lithiation method to the selective synthesis of 2,2-disubstituted alkanenitriles (8) using 2-ethylthioalkanenitriles (6) as starting materials (Eq. 2).



6 7 8

(2)

2-Ethylthioalkanenitriles (6) were easily obtained by the reaction of thioacetals with mercuric cyanide.5) The metallation of 6 was carried out in THF at 0 °C for 1 h using butyllitium as a base and the carbanion was treated with alkyl halide at -78 °C. After stirring overnight at room temperature, the alkylated product (7) was obtained in good yield (Table 2). The reductive alkylation of 7 proceeded successfully as was expected. The typical experimental procedure is as follows; to a THF (1.5 ml) - HMPA (0.2 ml) solution of 3-ethylthio-2-methyl-5-phenylpentane-3-carbonitrile (7) (124 mg, 0.5 mmol) was added a THF solution of tributylstannyllithium6) (0.65 mmol) at -78 °C. After stirring for 20 min, benzyl bromide (128 mg, 0.75 mmol) in THF(0.5 ml) was added and the reaction mixture was gradually warmed up to room temperature. After stirring overnight, the reaction was quenched by addition of 1 M NaOH aqueous solution and organic material was extracted with ether. The extract was dried over Na_2SO_4 and condensed under reduced pressure. The residue was chromatographed on silica gel (hexane-AcOEt) and 3-benzyl-2-methyl-5-phenylpentane-3-carbonitrile (8) (121 mg, 87%) was isolated.

In a similar manner, the reductive lithiation of various 2-ethylthioalkanenitriles (7) and the alkylation of the resulting α-cyano carbanions were examined (Table 2).

Table 2. The synthesis of 2,2-disubstituted alkanenitriles (8)

Alkylation of 6				Reductive alkylation of 7	
R^1	R^2	X	Yield4)/%	R^3X	Yield4)/%
Ph	CH_3	I	93,(94a))	CH_3I	89
				$CH_3(CH_2)_3Br$	81
				$CH_2{=}CHCH_2Br$	92
				$PhCH_2Br$	94,(94a))
CH_3CH_2	$CH_3(CH_2)_7$	Br	73	$CH_2{=}CHCH_2Br$	75
				$PhCH_2Br$	78
CH_3CH_2	$PhCH_2$	Br	74		
$(CH_3)_2CHCH_2$	$Ph(CH_2)_2$	Br	82	CH_3I	96
				$PhCH_2Br$	88
$(CH_3)_2CHCH_2$	CH_3	I	80		
$-(CH_2)_5-$		—	—b)	$PhCH_2Br$	77
				$Ph(CH_2)_2Br$	75

a) The yield of the product obtained by the reaction using the corresponding 2-phenylthioalkanenitrile.

b) Synthesized from cyclohexanone diethylthioacetal.

The results listed in Table 2 show that 2,2-disubstituted alkanenitriles (8) were synthesized in good to high yields without contamination of any by-product by the present method.

Since 2-ethylthioalkanenitrile (6) is prepared from thioacetal, it should be noted that the present investigation allowed the facile conversion of aldehyde to 2,2-disubstituted alkanenitrile (8).

Further study on the reductive lithiation of organosulfur compounds using tributylstannyllithium is now in progress.

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