Pergamon

Tetrahedron Letters, Vol. 37, No. 44, pp. 8015-8018, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01813-8

Synthesis of 2-Lithio-1,3-Diselenanes and 2-Lithio-1,3-Dithianes by Se/Li Exchange : First Successful Trapping of Axially Oriented 2-Lithio-1,3-Diselenanes.

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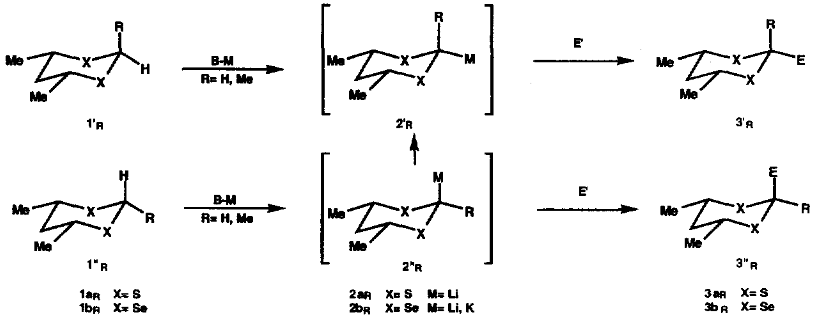
Abstract : Conformationally rigid 2-methylseleno-1,3-diselenanes bearing the methylseleno moiety in axial position react with butyllithiums at low temperature (-130°C) to produce 2-lithio-1,3-diselenanes bearing the lithium in axial position. These organometallics are configurationally stable at -130°C and slowly epimerise at -78°C. Deuteration occurs exclusively from the axial side if carried out at -130°C. 2-Methylseleno-1,3-dithianes behave differently since epimerisation of 2-lithio-1,3-dithianes almost immediately takes place already at -130°C. Copyright © 1996 Elsevier Science Ltd

It is firmly established that metallation of 1,3-dithianes **1a**[1] and 1,3-diselenanes **1b**[2] occurs regioselectively at C-2 on the equatorial rather than on the axial hydrogen. It has been also reported that reaction of the resulting 2-metallo-1,3-dithianes **2a** and 2-metallo-1,3-diselenanes **2b** with electrophiles leads to products **3'** bearing the incoming group invariably on the equatorial position (Scheme 1).[1,2] This therefore requires, in the case of **1"** an isomerisation of the related organometallic **2"** from the axial to the equatorial position leading to **2'** whatever is the nature and the bulkiness of the other substituent present at C-2. Trapping the 2-metallo-derivatives **2"** bearing the metal in the axial position, prior to its isomerisation, has been for long a challenge but all the efforts directed towards this end have been up to now unsuccessful.[1,2]

Scheme 1



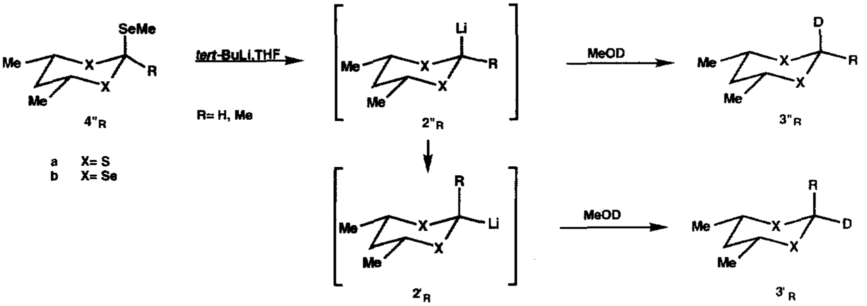
We now report that 2-lithio-1,3-dithianes **2a** and 2-lithio-1,3-diselenanes **2b** can be efficiently synthesized, *via* a Se/Li exchange, from 2-methylseleno-1,3-dithianes **4a** and 2-methylseleno-1,3-diselenanes **4b** and *tert*-butyllithium (Scheme 2).[5a] The reaction proceeds without competing hydrogen-lithium exchange at C-2 on **4a** and **4b** or selenium-lithium exchange on one of the endocyclic selenium of **4b** which would have otherwise led to the destruction of the heterocycle.[3]

Although the reactions have been carried out routinely at -78°C in THF, they already occur at much lower temperature (around -130°C or -116°C, 0.1 to 0.5 h) when performed in the Trapp mixture of solvents (THF-ether-pentane : 4-4-1).[4] The reaction involving 2-methylseleno-1,3-diselenanes **4b** proved to be highly stereoselective at these very low tempeatures and leads, after quenching with deuterated methanol, to the 2-deutero-4,6-dimethyl-1,3-diselenanes in which the deuterium atom has been stereoselectively introduced at position where the methylseleno was originally. Although the results involving the stereoisomers **4b'** bearing the seleno moiety in equatorial position are quite trivial,[2a,3,5b] those implying their stereoisomers **4b"** with the seleno moiety in axial position are remarkable.

As general trends the reaction is rather slow at -130°C, requires at least one hour to go to completion with the parent compound **4b"**$_H$ (Scheme 2, entries a,b) and occurs at a somewhat higher temperature (-116°C, Scheme 2, entry f)) with its higher homologue **4b"**$_{Me}$. 2-Lithio-4,6-dimethyl-1,3-diselenanes **2b"**$_H$ and **2b"**$_{Me}$ are both remarkably configurationally stable and retain their stereochemistry for a reasonably long time between -130 and -116°C (Scheme 2, entries b,f). They however slowly epimerise at -78°C (Scheme 2, entries d,e,g,h).[5b]

The reaction allows for the first time not only the formation of the axial lithiated derivative **2b"**$_H$, inaccessible by metallation of the diselenane**1b**$_H$,[2,3,5c] but also the trapping of axially lithiated derivatives **2b"**$_H$ and **2b"**$_{Me}$ which usually epimerise prior to reaction with electrophiles (Scheme 2).[2,3]

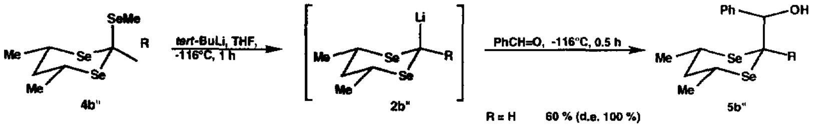
Scheme 2



Entry	Starting material	X	R	temperature	time	Product	Yield in **3** % (*3"/3'* ratio)
a	**4b"**$_H$	Se	H	-130 °C	0.2 h	**3b"**$_H$	25 % (99/1)
b	**4b"**$_H$	Se	H	-130 °C	1 h	**3b"**$_H$	85 % (98/2)
c	**4b"**$_H$	Se	H	-98 °C	1 h	**3b"**$_H$	90 % (95/5)
d	**4b"**$_H$	Se	H	-78 °C	0.1 h	**3b"**$_H$	90 % (70/30)
e	**4b"**$_H$	Se	H	-78 °C	1 h	**3b"**$_H$	80 % (40/60)
f	**4b"**$_{Me}$	Se	Me	-116 °C	1 h	**3b"**$_{Me}$	90 % (100/0)
g	**4b"**$_{Me}$	Se	Me	-78 °C	0.6 h	**3b"**$_{Me}$	80 % (50/50)
h	**4b"**$_{Me}$	Se	Me	-78 °C	1 h	**3b"**$_{Me}$	90 % (35/65)
i	**4a"**$_H$	S	H	-130 °C	0.1 h	**3a'**$_H$	91 % (1/99)

The axial organolithium compounds **2b"**, derived from **4b"** and *tert*-butyllithium also reacts efficiently with benzaldehyde and provides the corresponding β-hydroxy-selenoacetals with almost complete stereocontrol (Scheme 3). We have been however unable to trapp these organometallics with trimethylsilyl chloride.

Scheme 3



R = H 60 % (d.e. 100 %)
R = Me 68 % (d.e. 99 %)

As reported above 2-methylseleno-4,6-dimethyl-1,3-dithiane **4a"**$_H$ bearing the seleno moiety in axial position provides 2-lithio-4,6-dimethyl-1,3-dithiane on reaction with *tert*-butyllithium (Scheme 2, entry i). The reaction already proceeds at -130 °C and is very fast, faster than on its analogous 2-methylseleno-4,6-dimethyl-1,3-diselenane **4b"**$_H$ (Scheme 2, compare entries i and a). Surprisingly, epimerisation takes place almost instantaneously even at such very low temperature and delivers, after quenching with O-deuterated methanol, the 2-deutero-4,6-dimethyl-1,3-dithiane **3a'** with the deuterium atom in equatorial position.

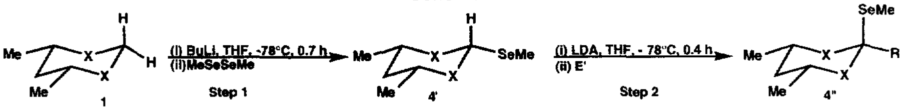
The quite high configurational stability of 2-lithio-4,6-dimethyl-1,3-diselenanes **2b"** compared to the one of the related 2-lithio-4,6-dimethyl-1,3-dithiane **2a"**$_H$ is unexpected.

We were rather surprised that the axially oriented 2-lithio-2,4,6-trimethyl-1,3-diselenane intermediate resulting from H/Li exchange between the all *cis*-2,4,6-trimethyl-1,3-diselenane **1b"**$_{Me}$ and *sec*-butyllithium immediately epimerises at -78°C[3] whereas the intermediate obtained by Se/Li exchange from 2-methylseleno-4,6-dimethyl-1,3-diselenane **4b"**$_{Me}$ exhibits an impressive conformational stability (Scheme 1, entries g,h). This leads us to suspect that these two intermediates are not identical and that in the second case a selenium ate complex could be responsible for holding the carbanion **2b"**$_{Me}$ in axial position until it is trapped by electrophiles.

Epimerisation of α-heterosubstituted organometallics is the subject of intensive work especially in the sulfur[1,6] and selenium series.[2,3,7] We would have expected, from the higher thermodynamic stability, that α-thioorganometallics would be configurationally more stable than their seleno analogs[8] and this apparently is not the case. Our results however match those recently reported by Hoffmann.[6a] The lower configurational stability of 2-lithio-1,3-dithianes compared to 2-lithio-1,3-diselenane can be due to the higher destabilizing effect on the carbanion **2"**, of the unshared electrons localized on the axial 3sp^3 orbitals of sulfur compared to those of related, more diffuse, 4sp^3 orbitals on selenium. We are currently checking experimentally these hypotheses.

2-Methylseleno-1,3-dithiane **4a"**$_H$ and 2-methylseleno-1,3-diselenanes **4b"**$_H$, **4b"**$_{Me}$ bearing the methylseleno moiety in axial position have been stereoselectively synthesized in two steps from 4,6-dimethyl-1,3-dithiane **1a**$_H$ and 4,6-dimethyl-1,3-diselenane **1b**$_H$ (Scheme 4).

Scheme 4

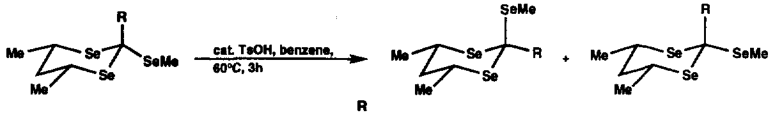


Entry	Starting material	X	Product	Yield in **4'** (%)	Step 2 E'	Product	R	Yield **4"** (%)
a	**1b**$_H$	Se	**4b'**$_H$	81 (100/0)	MeOH	**4b"**$_H$	H	95 (100/0)
b	**1b**$_H$	Se	**4b'**$_H$	81 (100/0)	MeI	**4b"**$_{Me}$	Me	93 (100/0)
c	**1a**$_H$	S	**4a'**$_H$	90 (100/0)	MeOH	**4a"**$_H$	H	93 (100/0)

This transformation involves the metallation-selenation of 1,3-dithiane **1a**$_H$ and 1,3-diselenane **1b**$_H$ ((i) *n*-BuLi, THF, - 78°C, 0.7 h, (ii) Me_2Se_2, -78°C to 20°C; step 1, Scheme 4) followed by metallation-protonation or methylation ((i) LDA, THF, - 78°C, 0.7 h, (ii) MeOH or MeI; step 2, Scheme 4) producing **4"**$_H$ or **4"**$_{Me}$ *via* a contrathermodynamic isomerisation of the organolithium intermediates.

In the course of this work we have observed a rapid acid catalyzed contrathermodynamic isomerisation of **4b'**$_H$, and **4b'**$_{Me}$ (TsOH, benzene, 60°C, 3h; Scheme 5) to **4b"**$_H$, and **4b"**$_{Me}$ respectively. Such isomerisation has been once noticed.[9]

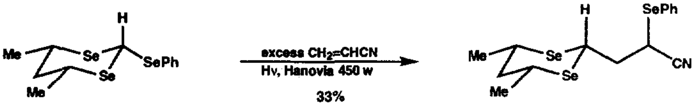
Scheme 5



R		
H	85	15
Me	62	38

We have also found that 2-phenylseleno-4,6-dimethyl-1,3-diselenane **5b"**$_H$, also prepared in the course of this work,[5a] was quite labile to light. We therefore investigated its behaviour towards acrylonitrile in the presence of light (20°C, Hanovia lamp, 450 watts) and observed the formation of a new selenide in which one acrylonitrile unit has been regioselectively inserted from the equatorial site (Scheme 6). We are working to determine the scope and limitations of this reaction whose first related example just appeared.[10]

Scheme 6



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5. (a) related results have been obtained from 2-phenylseleno- and 2-trimethylstannyl-4,6-dimethyl-1,3-diselenanes and alkyllithiums[5b] (b) We will report these results in the full paper (c) **1b**$_H$ is metallated on its more acidic equatorial hydrogen and therefore directly produces the equatorial lithio derivative **2b'**$_H$.
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The authors thank FRIA (Fonds pour la formation à la Recherche dans l'Industrie et l'Agriculture, Belgium) for supporting this work (Fellowship to L.D.).

(*Received in UK* 12 *July* 1996; *revised* 9 *September* 1996; *accepted* 13 *September* 1996)