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Reaction of 1,3-Diselenanes with Metal Amides

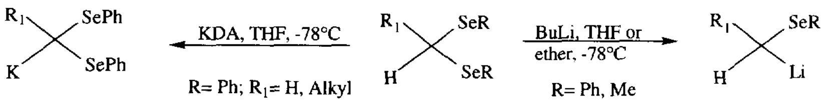
Alain Krief * and Laurent Defrère

Department of Chemistry, Facultés Universitaires Notre-Dame de la Paix, 61 rue de Bruxelles B-5000, NAMUR (Belgium).

Abstract : 1,3-Diselenanes are efficiently metallated by LDA or better by KDA. On conformationnally rigid derivatives, metallation is more efficient on equatorial hydrogen and leads to 2-metallo-diselenanes bearing the metal in equatorial position. Copyright © 1996 Elsevier Science Ltd

Metallation of selenoacetals is a rather difficult reaction. Alkyllithiums in THF, usually required for such reactions in related thioacetals, do not metallate selenoacetals and instead cleave one of the C-Se bond leading to α-selenoalkyllithiums almost quantitatively in both the phenylseleno- and methylseleno series.[1] Lithium amides in THF allow the metallation of the parent bis(phenylseleno)methane [1,2,3a] but are unable to metallate higher homologues. This can be achieved with lithium tetramethyl piperidide in THF-HMPA [3a] or better with KDA.[3b] However these basic systems are unable to metallate 1,1-bis(alkylseleno)alkanes even the parent compound (Scheme 1, R= Me, R_1= H).[3a]

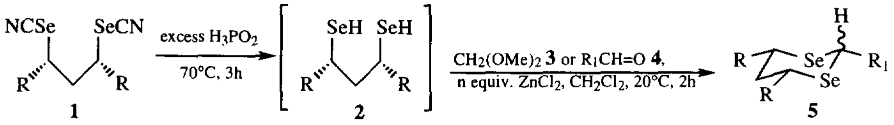
Scheme 1



1,3-Diselenanes [4] **5** belong to the 1,1-bis(alkylseleno)alkanes series but are expected, from the work of Corey and Seebach [5] and Eliel [6a-e] on related 1,3-dithianes, to be more acidic [6f] than the open chain derivatives. We report here our preliminary results on the synthesis and reactivity of 1,3-diselenanes **5** towards metalloamides.

The synthesis of such compounds has been carried out [4] from the diselenols **2**, prepared by reduction of the corresponding diselenocyanates **1** and dimethoxymethane **3**, benzaldehyde or acetaldehyde **4** in the presence of zinc chloride (Scheme 2).

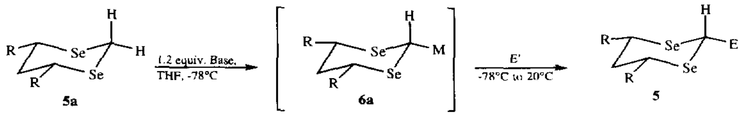
Scheme 2



Entry	R	Starting material	R_1	n equiv. $ZnCl_2$	Product	Yield in **5** % (*cis/trans*)
a	H	**3**	H	1	**5'a**	55
b	Me	**3**	H	1	**5"a**	55
c	Me	**4b**	Ph	0.5	**5"b**	78(100/0)
d	Me	**4c**	Me	0.5	**5"c**	72 (80/20)

The diselenane **5'a** is efficiently metallated with LDA (1.2 equiv., THF, -78°C, Scheme 3 entries a,b) but the closely related *cis*-4,6-dimethyl-1,3-diselenane **5"a**, which is expected to be conformationally rigid, requires KDA for complete metallation (1.2 equiv., THF -78°C, Scheme 3, compare entries c and d). Interestingly 2-lithio and 2-potassio 1,3-diselenanes **6"a** react stereoselectively with various electrophiles to provide the 1,3-diselenanes **5"** bearing the substituent in equatorial position (Scheme 3, entries c-g).

Scheme 3

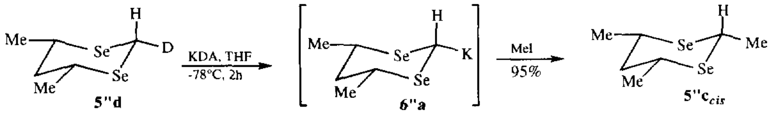


Entry	Starting material	R	Base	E'	Product	E	Yield in **5** % (*cis/trans* ratio)
a	**5'a**	H	LDA, 2h	MeI	**5'b**	Me	85
b	**5'a**	H	LDA, 2h	PhCH=O	**5'c**	PhCHOH	76
c	**5"a**	Me	LDA, 3.5 h	MeI	**5"c**	Me	50 (100/0)*
d	**5"a**	Me	KDA, 2h	MeI	**5"c**	Me	70 (100/0)
e	**5"a**	Me	KDA, 2h	MeOD	**5"d**	D	87 (100/0)
f	**5"a**	Me	KDA, 2h	(i) CO_2 (ii) CH_2N_2	**5"e**	CO_2Me	45 (95/5)
g	**5"a**	Me	KDA, 2h	PhSeSePh	**5"f**	PhSe	90 (98/2)

* The starting material (15 %) is also recovered.

It was also found that KDA reacts stereoselectively on the deuterium atom of 2-deutero-1,3-diselenane **5"d** bearing a deuterium atom in equatorial position in spite of an unfavorable isotope effect. Further reaction of the resulting 2-potassio-1,3-diselenanes **6"a** with methyl iodide leads to *cis*-2,4,6-trimethyl-1,3-diselenane **5"c**$_{cis}$ bearing the 2-methyl group in equatorial position and missing the deuterium atom there ((i) 1.2 equiv. KDA, -78°C, 2h (ii) MeI, -78°C to + 20°C, 95%, Scheme 4).

Scheme 4

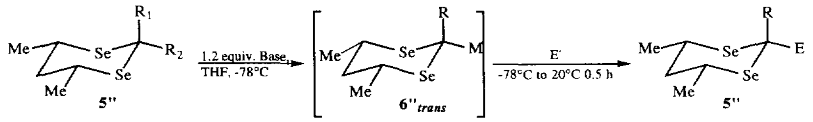


The preferred metallation on the equatorial hydrogen (deuterium) and the high stereoselectivity in favour of the product resulting from an equatorial attack of the electrophiles are consistant with the intermediate formation in all the cases of *cis*-2-metallo-4,6-dimethyl-1,3-diselenannyl derivatives bearing the metal in the equatorial position. These results are in concordance with those described on related 2-metallo *cis*-4,6-dimethyl-1,3-dithianes [6,7] and 1,3-dioxanes.[8] The strong preference of the unshared electron pair of the carbanion for the equatorial over the axial position has been explained on quantum chemical grounds, in terms of favorable and unfavorable orbital overlap, respectively.[9]

The same effects have been put forward [4d,f,10] to rationalize (i) the high tendency of butyllithium to react on the axial phenylseleno group of rigid 1,1-bis(phenylseleno)cyclohexanes (ii) the great aptitude of rigid 2-lithio-2-phenylselenocyclohexanes bearing the lithium atom in the equatorial position to rearrange to their axial epimer [4d,f,10a] and (iii) the epimerisation of α-thio- and α-seleno carbanions.[4d,10b]

Extension of this work shows that 2-phenyl- and 2-methyl-1,3-diselenanes **5"b** and **5"c** behave similarly. In both cases (i) the *cis*-stereoisomers **5"b**$_{cis}$ and **5"c**$_{cis}$ bearing the hydrogen in axial position proved to be more reluctant to metallation than their *trans*-stereoisomers **5"b**$_{trans}$ and **5"c**$_{trans}$ and (ii) the resulting organometallics exhibit a strong tendency to react from their equatorial site (Scheme 5).

Scheme 5

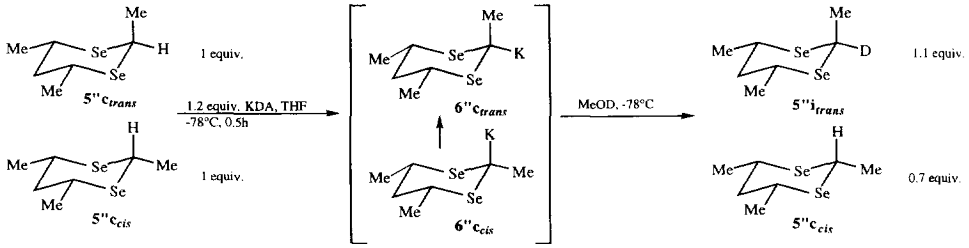


Entry	Starting material	R$_1$	R$_2$	Base	E'	Product	R	E	Yield in 5" % (*trans/cis* ratio)
a	**5"b**$_{cis}$	H	Ph	LDA, 0.5h	PhCH=O	SM	H	Ph	SM
b	**5"b**$_{cis}$	H	Ph	KDA, 0.5h	PhCH=O	**5"g**	Ph	PhCHO	75 (100/0)
c	**5"b**$_{cis}$	H	Ph	KDA, 0.5h	MeOH	**5"b**$_{trans}$	Ph	H	98 (99/1)
d	**5"b**$_{cis}$	H	Ph	KDA, 0.5h	MeI	**5"h**	Ph	Me	100 (100/0)
e	**5"b**$_{trans}$	Ph	H	LDA, 0.25h	MeI	**5"h**	Ph	Me	95 (98/2)
f	**5"c**$_{cis}$*	H	Me	LDA, 1h	MeOD	SM	H	Me	SM
g	**5"c**$_{cis}$*	H	Me	KDA, 1h	MeOD	**5"i**$_{trans}$	Me	D	75 (100/0)
h	**5"c**$_{cis}$*	H	Me	KDA, 1h	MeOH	**5"c**$_{trans}$	Me	H	95 (98/2)
i	**5"c**$_{trans}$	Me	H	LDA, 1h	MeOD	SM	Me	H	SM
j	**5"c**$_{trans}$	Me	H	KDA, 1h	MeOD	**5"i**$_{trans}$	Me	D	75 (100/0)

* a 80/20 mixture of cis/trans stereoisomers has been used in this experiment (see results in Scheme 2).

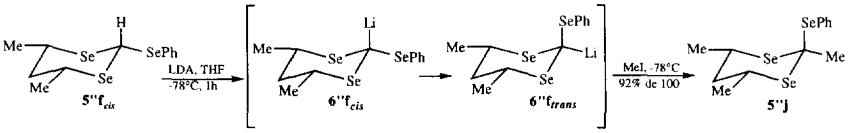
Thus, whereas LDA metallates **5"b**$_{trans}$, KDA (a stronger base) is required for successful metallation of its **5"b**$_{cis}$ stereoisomer (Scheme 5, entries e,b; compare entries e to a). Furthermore although both **5"c**$_{cis}$ and **5"c**$_{trans}$ required KDA to be metallated (Scheme 5, entries g,j), **5"c**$_{trans}$ is almost exclusively metallated in a competition experiment in which a one to one mixture of **5"c**$_{trans}$ / **5"c**$_{cis}$ (1 equiv. each) is reacted with a slight excess of KDA (1.2 equiv., Scheme 6).

Scheme 6



We have also reacted *cis*-2-phenylseleno-4,6-dimethyl-1,3-diselenane **5"f**$_{cis}$ (prepared as disclosed in Scheme 3, entry g) with LDA. Metallation occurs very efficiently and provides, on further reaction with methyl iodide, 2-methyl-2-phenylseleno-4,6-dimethyl-1,3-diselenane **5"j**$_{trans}$ bearing the phenylseleno group in axial position with complete control of the stereochemistry (Scheme 7).

Scheme 7



It is interesting to notice that the formation of **5"j** requires the epimerisation of the 2-lithio-2-phenylseleno-4,6-dimethyl-1,3-diselenane **6"f**$_{cis}$ formed intermediarily to its **6"f**$_{trans}$ stereoisomer although it brings the quite bulky phenylseleno group in axial position. These results are expected on the ground of thoses described above. They however differ from the ones reported on the related cyclohexyl system missing the two selenium atoms in which the lithium strongly prefers to lie in axial position.[4d,f,10a] They suggest that the dispersion of the carbanion on the diselenanyl framework is better than on the phenylseleno group on **6"f**. It is unclear at present if this is the result of the competition between additive effects of the two seleno groups in the cycle compared to the single effect of the phenylseleno moiety. Work is in progress to clarify this point.

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