

Stereoselective Synthesis and Reactions of 1-Seleno-4-tert-Butyl Cyclohexyllithiums

A. Krief*, G. Evrard*, E. Badaoui, V. De Beys and R. Dieden

Department of Chemistry, Facultés Universitaires Notre-Dame de la Paix, 61 rue de Bruxelles,
B-5000 Namur (BELGIUM)

The axial C-Se bond of seleno- and mixed selenoacetals derived from 4-tert-butyl cyclohexanones exhibit a high tendency to be cleaved by n-butyllithium. The resulting 1-seleno-4-tert-butyl cyclohexyllithiums are selectively protonated or selenylated via axial attack.

We recently described¹ that 1,1-bis(phenylseleno)-4-tert-butyl cyclohexane **1a** reacts with n-butyllithium to provide, after hydrolysis, 1-(phenylseleno)-4-tert-butyl cyclohexane **4a** (trans/cis : 96 / 4) with almost complete stereocontrol (Scheme 1 entry I). Although this result implies that axial protonation of the intermediately formed 1-lithio-4-tert-butyl cyclohexane has taken place, it does not tell which one of the two phenylseleno groups is cleaved by n-butyllithium.

We now report that the reaction takes place almost exclusively on the axial phenylseleno group and delivers the corresponding 1-seleno-4-tert-butyl cyclohexyllithium possessing an axial carbon lithium bond. We have for that purpose performed the above mentioned reaction on 1-phenylseleno-1-perdeuterophenylseleno-4-tert-butyl cyclohexane **1a'** bearing the perdeuterophenylseleno moiety in the axial position and have directly analysed the crude mixture of selenides by GCMS². We found that the phenylseleno group remains attached to the cyclohexyl moiety whereas the perdeuterophenyl group becomes part of the butyl selenide **3a'** concomitantly formed (Scheme 1 entry III).

The same reaction performed on 1-perdeuteromethylseleno-1-methylseleno-4-tert-butyl cyclohexane **1b'** bearing the perdeuterated methylseleno moiety in the axial position leads to similar results since 1-methylseleno-4-tert-butyl cyclohexane **4b** (trans/cis : 96 / 4) without a perdeuteromethylseleno substituent is produced almost quantitatively³ (Scheme 1 entry VI) under similar conditions.

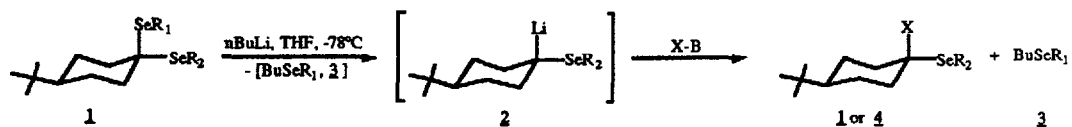
In order to get further information on this spectacular behaviour we looked at the reactivity of the two stereoisomeric 1-methylseleno-1-phenylseleno-4-tert-butyl cyclohexanes **1c** and **1d** towards n-butyllithium. We have in fact recently described⁴ that this reagent usually cleaves selectively the C-SeMe bond of alkanes geminally substituted by a phenylseleno and a methylseleno group providing thus the corresponding α -phenylselenoalkyllithium which is expected to possess the more stabilised of the two selenoalkyllithiums potentially available.^{1,4} Although trans 1-phenylseleno-4-tert-butyl cyclohexane **4a** is expected to be formed when the above mentioned protocol is performed on the mixed selenoacetal **1c** bearing the methylseleno moiety in the axial position, and that in fact proved to be the case (**4a**, trans/cis : 97 / 3, Scheme 1 entry VII), the situation should be different when its stereoisomer **1d** is involved since two effects should work in opposite directions. The cleavage of the axial C-SePh bond expected on the basis of the above mentioned results should

provide the 1-lithio-1-methylseleno-4-tert-butyl cyclohexane **2b** which possesses the less stabilized carbanionic centre whereas the cleavage of the equatorial C-SeMe bond should provide 1-lithio-1-phenylseleno-4-tert-butyl cyclohexane **2a'** with the more stabilized carbanionic centre but which contains an equatorial lithium atom which, from the above discussion, would appear to be the less favourable. We in fact found (Scheme 2) that cleavage of the equatorial C-SeMe bond occurred predominantly (**2a/2b** : 80 / 20) and that the resulting 1-phenylseleno-4-tert-butyl cyclohexyllithium **2a'** rearranged almost instantaneously ⁵ to its stereoisomer **2a**, in which the lithium atom is axial, prior to hydrolysis leading finally to 1-phenylseleno-4-tert-butyl cyclohexane **4a** (trans/cis : 96 / 4) and 1-methylseleno-4-tert-butyl cyclohexane **4b** (trans/cis : 96 / 4).

The mixed selenoacetals required for this work have been prepared by selenenylation of the corresponding 1-lithio-1-seleno-4-tert-butyl cyclohexanes **2**. This reaction proved to be almost completely stereoselective, the entering seleno moiety being introduced from the axial direction. Thus 1-perdeuterophenylseleno- and 1-methylseleno-1-phenylseleno-4-tert-butyl cyclohexane **1a'** and **1c** have been prepared from 1,1-bis(phenylseleno)-4-tert-butyl cyclohexane **1a** by sequential reaction with n-butyllithium in THF and with perdeuterodiphenyldiselenide ^{6a} or dimethyldiselenide (Scheme 1 entries I and II) whereas **1b'** and **1d** have been synthesized from 1,1-bis(methylseleno)-4-tert-butyl cyclohexane and diperdeuteromethyldiselenide ^{6b} and diphenyldiselenide respectively (Scheme 1 entries IV and V). The ⁷⁷Se NMR spectra of the two mixed selenoacetals **1c** and **1d** of different origin were remarkably different (see table). In fact, as previously reported by Duddeck ^{8a}, an axial PhSe group is about 130 ppm more shielded than its equatorial counterpart. The same proves to be valid for MeSe groups. In addition, replacement of a methyl group by a phenyl group results generally in a deshielding of ~220 ppm ^{8b}. Furthermore the structure of **1c** (m.p.= 50-51°C) has been unambiguously determined by X-ray crystallography ⁹ (figure). Finally the structure of the mixed acetal **1a'** has been assessed by analogy to the above mentioned ones assuming ¹⁰ that diperdeuterophenyldiselenide reacts via an axial attack as does dimethyldiselenide with 1-lithio-1-phenylseleno-4-tert-butyl cyclohexane **2a**.

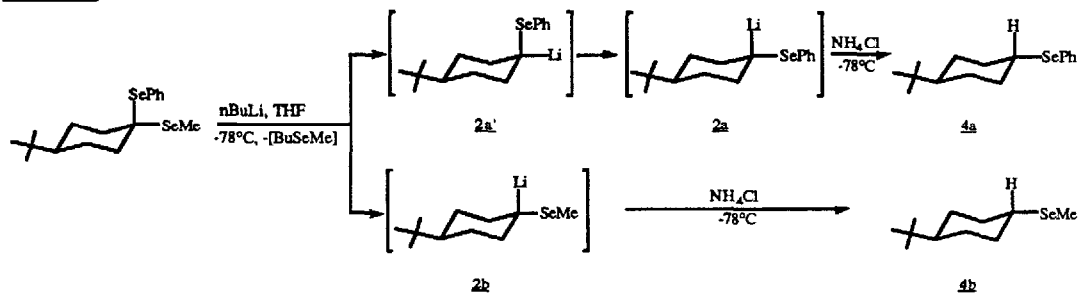
Little is known ¹¹, except for cyclopropyllithiums ¹¹, about the stereochemistry of conformationally rigid cycloalkyllithiums. It has however been described that menthyllithium ^{12a,b}, generated from menthyl- or neomenthyl chloride and lithium metal in refluxing pentane, bearing an equatorial C-Li bond is present in significant quantities regardless of the halide used for its preparation and that carbonation, deuteration and bromination with dibromoethane proceeds with predominant retention of configuration whereas halogenation with halogens results in significant and often predominant inversion of configuration. 1-Lithio-4-tert-butyl-cyclohexane available from the corresponding chloride behaves ^{12b,c} similarly. It has been suggested that in these species, the bulky chelated lithium lies in the equatorial position. However, as has been shown in this work 1-lithio-1-seleno-4-tert-butyl cyclohexanes with the lithium in the axial position are produced almost exclusively under kinetic control from seleno- or mixed selenoacetals **1a**, **1a'**, **1b**, **1b'**, **1c** and under thermodynamic control from the mixed selenoacetal **1d** and that they react almost exclusively from axial attack with ammonium chloride and diselenides. It would be surprising if only steric factors are responsible for such behaviour. We are currently investigating the stereochemical behaviour of 1-lithio-4-tert-butyl cyclohexanes with various substituents at C₁ in order to supply a reasonable solution to this behaviour.

Scheme 1



Entry	R ₁	R ₂	2	3	X-B = H-NH ₃ Cl		X-B = R ₁ Se-SeR ₁	
					4	X	R ₁	Yield%
I	1a	C ₆ H ₅	2a	3a	4a	H	1a'	C ₆ D ₅ 84%
II	1a'	C ₆ D ₅	2a	3a'	4a	H	1c	CH ₃ 87%
III	1b	CH ₃	2b	3b	4b	H	1b'	CD ₃ 81%
IV	1b'	CD ₃	2b	3b'	4b	H	1d	C ₆ H ₅ 80%
V	1c	CH ₃	2a	3b	4a	H		
VI	1c	C ₆ H ₅	2a	3b	4a	H		

Scheme 2

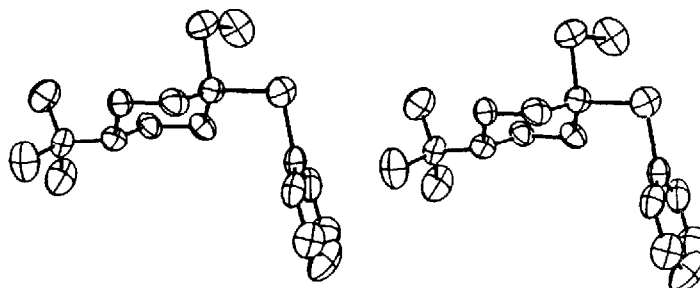


Table

X	R ₂	δX	δSeR		
				1a	1b
SePh	Ph	420.0	558.5		
SeMe	Me	178.7	311.2		
SeMe	Ph	199.3	541.4		
SePh	Me	406.0	341.5		
H	Ph	-	406.6		
H	Me	-	181.9		

⁷⁷Se chemical shifts in ppm at 293°K., in CDCl₃, Me₂Se being used as the reference

Figure



References

1. A. Krief, W. Dumont, M. Clarembeau, G. Bernard and E. Badaoui, *Tetrahedron* **45**, 2005 (1989).
2. These analyses have been performed on an Hewlett-Packard GC/MS 5995A fitted with a HP-17 (crosslinked 5% methyl silicon gum phase) column (25 m x 0.2 mm x 0.33 μm), He as carrier gas, flow rate : 1ml /mn.
3. Some doubt remains about the butylselenide which might contain 10-15 % of CH_3 besides a large quantity of CD_3 . Work is in progress using a more sophisticated GC/MS system to understand this surprising result.
4. A. Krief, W. Dumont, M. Clarembeau and E. Badaoui, *Tetrahedron* **45**, 2023 (1989).
5. This reaction has also been followed at -78°C by ^{77}Se NMR. It is surprisingly slower than the related reactions described above. We have observed the 1-lithio-1-phenylseleno-4-tert butyl cyclohexane bearing the lithium exclusively in axial position. (δ : 467.4 ppm, THF-hexane) as well as the corresponding methylseleno analogue (δ : 229.3 ppm, THF-hexane).
- 6 a. Prepared by oxidation 7^a of perdeuterophenylselenol itself synthesised 7^b from perdeuterobromobenzene (Janssen Chimica) and elemental magnesium and selenium.
b. Prepared in 40% yield from perdeuteromethyl iodide, lithium borohydride-methanol and elemental selenium in DMF. 7^c
- 7 a. A. Krief, A.F. De Mahieu, W. Dumont and M. Trabelsi, *Synthesis*, 131, (1988).
b. D.C. Foster, *Organic Reaction*, Coll. Vol. 3, 771 (1955).
c. M.Trabelsi, unpublished results from our laboratory.
- 8 a. H. Duddeck, P. Wagner and S. Gegner, *Tetrahedron Lett.* **26**, 1205, (1985)
b. N.P. Luthra and J.D. Odum in : "The Chemistry of Organic Selenium and Tellurium Compounds", S. Patai and Z. Rappoport Ed., J. Wiley & Sons Ltd. (1986), vol. I, ch. 6, pp. 189-241
- 9 a. Crystal data : $\text{C}_{17}\text{H}_{26}\text{Se}_2$, $M_R = 388$, monoclinic, space group $\text{P}2_1/c$, $a = 18.970(11)$, $b = 8.728(15)$, $c = 11.280(6)$ \AA , $\beta = 107.027(24)^\circ$, $V = 1786$ \AA^3 , $Z = 4$, $D_x = 1.443$ g.cm^{-3} , X-ray data were collected using an Enraf-Nonius CAD-4 diffractometer, and Mo-K α radiation ($\lambda = 0.71069$ \AA), with 2053 unique observed reflections [with $I > 1.9 \sigma(I)$] having $2\theta < 52^\circ$. The structure was solved by direct method SHELX-86 and refined by full-matrix least squares to a current residual R of 0.04 (SHELX-76) 9b . The atomic coordinates for this work are available on request from the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CBE 1EW, Great Britain.
b. G.M. Sheldrick, SHELX-76, "Program for crystal structure determination", University of Cambridge, England (1976).
10. The neutron diffraction of $1a'$ will be performed soon.
- 11 a. D.J. Cram in "Fundamentals of Carbanion Chemistry : Organic Chemistry, a series of monographs", A.T. Blomquist Ed., New York (1965).
b. B.J. Wakefield in "The Chemistry of organolithium Compounds", Pergamon Press, Oxford, England (1974).
- 12 a. W.H. Glaze and C.M. Selman, *J. Org. Chem.* **33**, 1987 (1968).
b. W.H. Glaze, C.M. Selman, A.L. Ball and L.E. Bray, *J. Org. Chem.* **34**, 641 (1969).
c. W.H. Glaze and C.M. Selman, *J. Organometal. Chem.*, **11**, P3 (1968).

(Received in UK 25 August 1989)