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γ-Silyloxy-Benzyllithiums : Stereochemistry of the Retro-[1,4]-Brook Rearrangement

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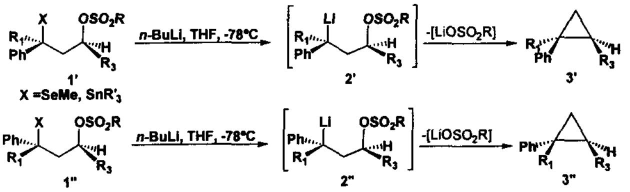
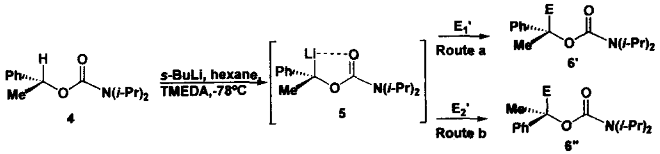
Abstract : Although γ-sulfonyloxy-benzylselenides react with butyllithium to produce stereospecifically aryl cyclopropanes, the corresponding γ-silyloxy-benzylselenides lead to a stereoisomeric mixture of γ-hydroxy-α-silyl-benzylselenides via the retro-[1,4]-Brook rearrangement. Apparently the intermediate benzyllithiums are alkylated before epimerisation takes place in the first case, whereas in the second one epimerisation occurs prior to the silyl group migration.

The stereochemical stability of benzyllithiums has attracted wide interest over the last decade.[1] Although it is now well admitted that these organometallics are usually *configurationally unstable*, some stereoselective reactions have been reported.[1e-4] This is particularly the case of (i) benzyllithiums, unsubstituted in β-position and bearing a sulfonyloxy-group in γ-position,[5a,b] which produce in THF at -78°C, arylcyclopropane derivatives with *inversion of configuration* at the two substituted carbons (Scheme 1),[2] (ii) carbamoyloxy-substituted benzyllithiums (Scheme 2),[1e,3,5b,c] which react in alkanes or diethyl ether in the presence of TMEDA (a) *with retention of configuration* on methyl carboxylates, acid anhydrides, allyl chloride or methanol but (b) with *inversion of configuration* on acid chlorides, carbon dioxide or -disulfide, isopropyl isocyanate, trimethyltin chloride, trimethylplumbyl chloride and probably trimethylsilyl chloride (iii) α-silyloxy-benzyllithiums (Scheme 3),[4,5c] which produce, in THF at -78°C, α-hydroxy-benzylsilanes with net *retention of configuration*.

Scheme 1

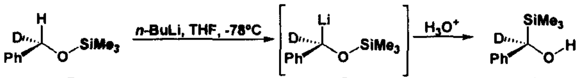


Scheme 2



In memoriam Prof. Gerrit L'abbé, KUL, Belgium.

Scheme 3



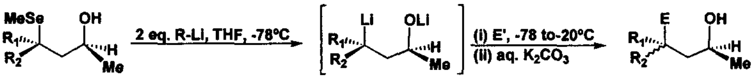
7 8 9

We now report our results concerning the stereochemical course of reactions involving benzyllithiums bearing an alkoxy or a silyloxy group in γ-position. These intermediates have already been described by Kuwajima,[6] our group[2] (Scheme 1a) and by Normant and Marek.[7]

For that purpose, a series of γ-hydroxy-benzylselenides **10** have been prepared according to our published procedure involving epoxide ring opening by benzyl metals.[2] Their reaction with butyllithium (2 eq.) or better with methyllithium (1 eq), to ensure selective alkoxide formation, then butyllithium (1 eq.) to cleave the C-Se bond of the resulting alkoxide (THF-hexane, -78°C, 0.5 h), led to the γ-alkoxy-benzyllithiums **11**. These on further reaction with an electrophile (1.1 eq., -78 to 20°C, 0.5 h), produced the alcohols **12** after quenching with an aqueous saturated solution of sodium carbonate (Scheme 4).

Performing the reaction with an excess of trimethylsilyl chloride (Scheme 4, entries a-c) led to the γ-hydroxy-benzylsilanes **12a** and **12b**, suggesting that the intermediates γ-alkoxy-benzylsilanes are not silylated under our experimental conditions.

Scheme 4



10 11 12

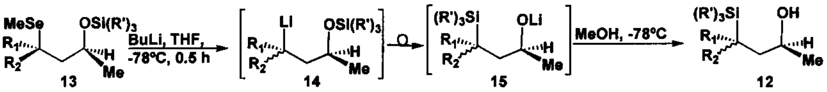
Entry	R_1	R_2	Starting material	d.e.	RLi	E'	E	Product	Yield in **12** (*d.e.*)
a	Ph	Me	**10a'**	> 98	(2 *n*-BuLi)	Me_3SiCl	Me_3Si	**12a**	73 (10)
b	Me	Ph	**10a"**	> 98	(2 *n*-BuLi)	Me_3SiCl	Me_3Si	**12a**	59 (10)
c	Ph	MeSe	**10b**	-	(MeLi + *n*-BuLi)	Me_3SiCl	Me_3Si	**12b**	68 (> 98)
d	Ph	MeSe	**10b**	-	(MeLi + *n*-BuLi)	$Br\text{-}(CH_2)_3\text{-}CH{=}CH_2$	$(CH_2)_3\text{-}CH{=}CH_2$	**12c**	85 (> 98)
e	Ph	MeS	**10d**	60	(MeLi + *n*-BuLi)	$Br\text{-}(CH_2)_3\text{-}CH{=}CH_2$	$(CH_2)_3\text{-}CH{=}CH_2$	**12d**	95 (96)
f	Ph	MeO	**10e**	0	(MeLi + *t*-BuLi)	$Br\text{-}(CH_2)_3\text{-}CH{=}CH_2$	$(CH_2)_3\text{-}CH{=}CH_2$	**12e**	95 (94)

The results described in Scheme 4 clearly show that epimerisation took place with all benzyllithiums **11** prior to trapping. Those derivatives bearing a methyl group on the carbanionic center led to a one to one mixture of stereoisomers (Scheme 4, entries a, b) whereas those bearing a heteroatomic moiety at the same center, gave almost a single stereoisomer (Scheme 3, entries c-f) whose relative stereochemistry, except that of **12e** (see below), has not yet been firmly established. The stereoselective synthesis of **12e** from a diastereoisomeric mixture of **10e** implies that the α-methoxy benzyllithium intermediate **11e** completely epimerises (Scheme 4, entry f). This contrasts with the results involving other α-alkoxy-alkyllithiums, missing the phenyl substituent on the carbanionic center, which have been proved to be configurationally stable.[8]

The high propensity of γ-alkoxy-benzyllithiums to epimerise (Scheme 4), reported above, also contrasts with the highly stereospecific reaction reported for the related (i) cyclopropanation of γ-sulfonyloxy-benzyllithiums (Scheme 1)[2] and (ii) Wittig rearrangement (Scheme 3).[4] We suspected that the intramolecular nature of these reactions was responsible for trapping the benzylic center prior to its epimerisation. We therefore decided to look at the behavior of related γ-silyloxy-benzyl selenides toward butyllithiums which were expected to provide γ-hydroxy-benzylsilanes *via* the well known retro-[1,4]-Brook rearrangement.[9-12] We hoped that it would occur intramolecularly,[10a,g,j] and with retention of configuration at the carbanionic center, as it has been often observed and therefore that the intermediate[9-12] γ-silyloxy-benzyllithiums **14** would be configurationally stable in reference to the time scale of the subsequent rearrangement.[10a,d]

We found that the rearrangement, except in rare cases, took place very rapidly (THF, -78°C, < 0.5 h) and led, after hydrolysis, to γ-hydroxy-benzylsilanes[13] in very good yield but as a mixture of stereoisomers (Scheme 5). Lowering the temperature did not significantly affect the stereochemical course of the rearrangement but slowed down the reaction [**13e** (d.e. 0%) generates at -110°C for 2h, **12e** (d.e. 100 %) in 18 % yield; compare to Scheme 5, entries c or d].

Scheme 5

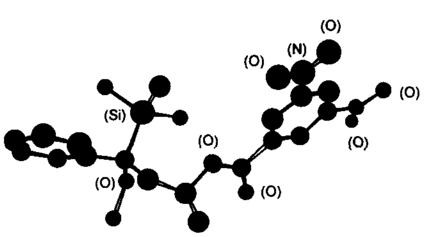


Entry	R_1	R_2	R'	Starting material	d.e.	BuLi	Product	Yield in **12** (d.e.)
a	Ph	Me	Me	**13a'**	> 98	*n*-	**12a**	80 (54)
b	Me	Ph	Me	**13a"**	> 98	*n*-	**12a**	81 (56)
c	Ph	MeO	Me	**13e'**	> 98	*t*-	**12e**	61 (72)
d	MeO	Ph	Me	**13e"**	> 98	*t*-	**12e**	57 (76)
e	Ph	H	Me	**13f'**	> 98	*n*-	**12f**	86 (26)
f	H	Ph	Me	**13f"**	> 98	*n*-	**12f**	77 (26)
g	Ph	Et	Me	**13g**	> 98	*n*-	**12g**	44 (32)[a1]
h	Ph	Et	Et	**13h**	0	*n*-	**12h**	0[a2]

(a) The product resulting from the protonation of the intermediate benzyllithium (1) is observed besides some unreacted starting material or (2) is exclusively produced (96%; d.e. : 0 %)

The reaction tolerates several substituents on the carbanionic center, including the methoxy one (Scheme 5, entries c, d), but does not occur with those bearing a closely related methylseleno or a phenylthio substituent on the same site. Raising the temperature in the latter cases led to the decomposition of the starting materials. The lower reactivity of these S/Se derivatives, parallels the higher stabilization of the Se/S-substituted carbanion compared to the O-substituted one. We also found that the rearrangement is affected by steric constraints at silicon, as reported in some cases.[11,12] For example, although the rearrangement occurred, already at -78°C, on the 3-phenyl-3-methylseleno-5-trimethylsilyloxy-hexane **13g**, (Scheme 5, entry g), it was not effective, under the same conditions, on the 5-triethylsilyloxy-derivative **13h** (Scheme 5, entry h) which however reacted at higher temperature (-78°C, 0.5h then -50°C, 1.5h, **12h** : 72%, d.e. 100).

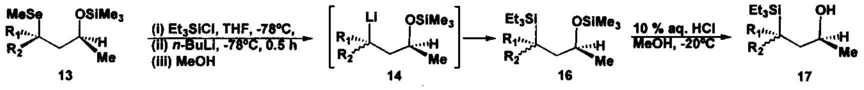
We interestingly found that the retro-Brook rearrangement of any one of the two stereoisomers of α-methoxy-γ-silyloxy-benzyl selenide **13e** (Scheme 5, entries c, d) led mainly to the α-methoxy-benzyl silane **12e'** whose structure has been unambiguously assigned from the X-ray crystallography of its dinitrobenzoate (m.p. 112°C) as shown below.



The fact that the reaction is not stereospecific (Scheme 5) implies an epimerisation at the benzylic carbon. This can formally occur on the γ-silyloxy-benzyllithium intermediates **14** before the migration of the silyl group or during the retro-Brook rearrangement. In order to have some precise details on the rate of the retro-Brook rearrangement, we have reacted, each stereoisomer of 2-methylseleno-2-phenyl-4-triethylsilyoxy-pentane **13a** with *n*-butyllithium, in the presence of trimethylsilyl chloride (THF, -78°C, 0.5 h, Scheme 6), with the hope of trapping the benzyllithium intermediate **14a** before it rearranges.

We obtained the 2-trimethylsilyl-2-phenyl-4-triethylsilyoxy-butane **16a**, free from **12a** and as a mixture of stereoisomers. Further acid hydrolysis of each batch of **16a** confirms our expectations since it produces **17a** who's ^{1}H NMR does not exhibit a trimethylsilyl peak. These results clearly show that intermolecular reaction leading to **16a** exclusively occurs and that it is much faster than the retro-Brook rearrangement. It is obvious, taking into account the results described in Scheme 4, that epimerisation of at least the benzyllithiums **14a** is taking place before the retro-Brook rearrangement occurs and therefore we could not have an indication on the stereochemistry of the rearrangement itself.

Scheme 7



Entry	R_1	R_2	Starting material	d.e.	Yield in **16a** % (d.e.)	Yield in **17a** % (d.e.)
a	Ph	Me	**13a'**	80	83 (16)	81 (20)
b	Me	Ph	**13a"**	100	83 (22)	83 (26)

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