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STEREOCHEMISTRY OF THE C_3 ADDITION OF 1-LITHIO 1,1-BIS METHYLSELENOALKANES TO METHYL CYCLOHEXENONES

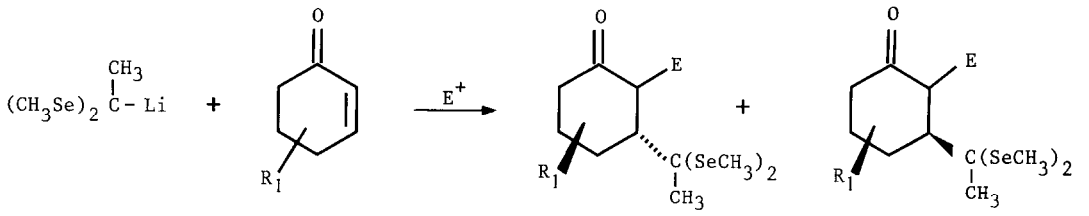
J. Lucchetti and A. Krief*

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

The presence of DME or HMPT allows the C_3 regio and stereoselective introduction of 1,1-bis methylselenoalkanes to methyl cyclohexenones. The resulting compounds have been stereoselectively transformed to 3-ethyl methyl cyclohexanones.

Selective introduction of organometallics at the C_3 site of enones is of great synthetic value. This has been achieved by addition of copper salts [1] for organometallics bearing an hydrocarbon residue and more recently, for α-heterosubstituted organolithiums [2] which do not bear an extra stabilizing group, by use of solvent which strongly solvates the metal (e.i. HMPT and DME in some cases).

Nothing is known at the present time about the stereochemistry of the addition of the last species to alkylsubstituted enones. We report here our preliminary observations concerning the stereochemistry of the addition of 1,1-bis (methylseleno) 1-lithio ethane 1 (prepared from trismethylseleno ethane and n-BuLi in THF or DME at -78°C)[3] to methyl cyclohexenones 2 [respectively in THF/HMPT (1.1 eq) (method A) or in DME (method B) at -78°C and quenching with aqueous NH_4Cl at -78°C] [3b].



1 2 3' 3"

Except for the 3-methyl cyclohexenone, the C_3 adducts are isolated in 60 to 76% yield (Table) and little if any allylic alcohols resulting from the competing C_1 attack is formed when method A is used. A good to high stereoselectivity (ranging from 68-32 to 99-1) is observed (^1H, ^{13}C-NMR, | GC |[2] OV1) depending upon the nature of the starting enone (Table). The experimental conditions [e.i. solvent change THF/HMPT or DME), temperature used (-110°C,

-78°C, -45°C or -78°C to 20°C) and the time of the reaction (3-5 seconds or 10 min.)] do not seem to affect the ratio of isomers present after quenching.

We have also prepared the δ-ketoacetals 3a by reaction of 1 on cyclohexenone in THF/HMPT followed by the trapping of the resulting lithio enolate [4] with methyl iodide (5 eq) in THF containing HMPT (5 eq, 0°, 1hr)[5]. The product consists quite exclusively of one single stereoisomer 3a' which is the minor isomer (1%) obtained from the reaction of the same organometallic 1 on 2-methyl cyclohexenone (Table, entries 1 and 2).

The trans isomer 3' is the major one in case of 4- and 5-methyl-cyclohexenones (Table, entries 4, 5) and on methylation of the enolate formed by reaction of 1 with cyclohexenone (Table, entry 1).

The cis isomer 3" being mainly formed in the case of 2- and 6-methylcyclohexenones (Table, entries 2, 6).

The stereochemical assignments have been performed on 3-ethyl-methyl-cyclohexanones 4 regio and stereoselectively prepared by tributyltin hydride reduction of the selenoacetal moiety of the δ-keto selenoacetals 3 [Bu_3SnH, 3 eq, AIBN (0.12 eq), toluene, 80°C, 0.3 hr][3,6] (see Table).

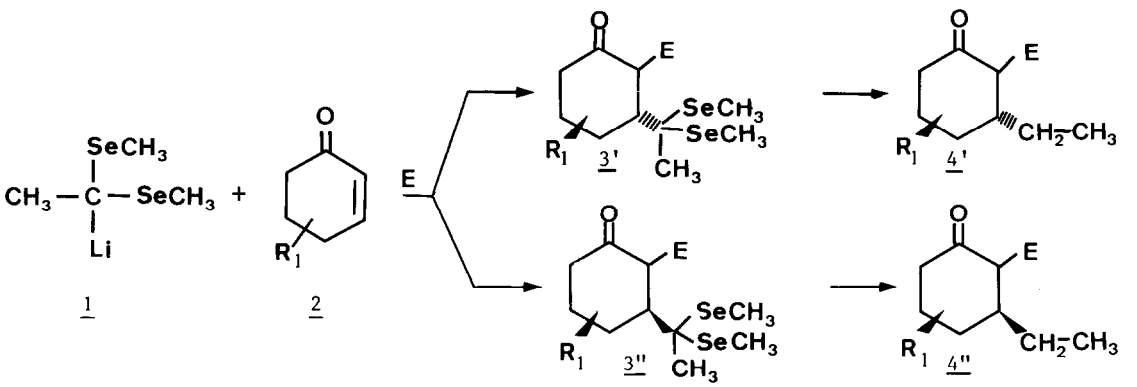
These assignments have already been done by Rivière [7,11] in the case of 3-ethyl-4-methyl cyclohexanone 4b and we have correlated (see scheme II) the 3-ethyl-5-methyl-cyclohexanone 4c with the 3,5-dimethyl cyclohexanone 7, the structure of which was already determined by House [8]. Thus, the enolate 5 prepared from 5-methyl cyclohexenone and bis (methylseleno)-methyllithium (THF/HMPT, 1.1 eq, -78°C) was simultaneously transformed (scheme II) to the previously known 3,5-dimethylcyclohexanone 7 [by hydrolysis to 6 and selective reduction of the selenoacetal moiety] and to 3-ethyl-5-methyl-cyclohexanone 4c [by trapping with chlorotrimethylsilane, cleavage of the selenoacetal moiety, selective methylation of the resulting α-selenoalkyllithium [9], further hydrolysis of the silylenol ether and reduction of the selenyl moiety].

The isomeric ratios of 7 and 4c are identical 7'/7" = 4c'/4c" : 92/8) and the derivatives 4c of different origin are identical.

Finally 3-ethyl-2-methyl cyclohexanone 4a and 3-ethyl 6-methyl cyclohexanone 4d of various origins have been subjected to epimerization reactions (H_2SO_4/acetone/60°, 0.05 hr) and we have assigned the trans stereochemistry to the major isomer : pure 4a' and 4a" (Table, entries 1 and 2) produced a 77/23 ratio of 4a'/4a" while pure 4d' and 4d" (Table, entry 6) gave a 68/32 ratio of 4d'/4d".

The reactions described allow the highly stereoselective introduction of groups bearing a latent fonctionality at the C_3 site of an enone [3b]. Moreover, the cleavage of the carbon-selenium bond in 8 (scheme II) is of particular interest since it is the first reported cleavage of a functionalized selenoacetal. Work is now in progress to use the potentiality of the reported reactions for the synthesis of natural products.

SCHEME I

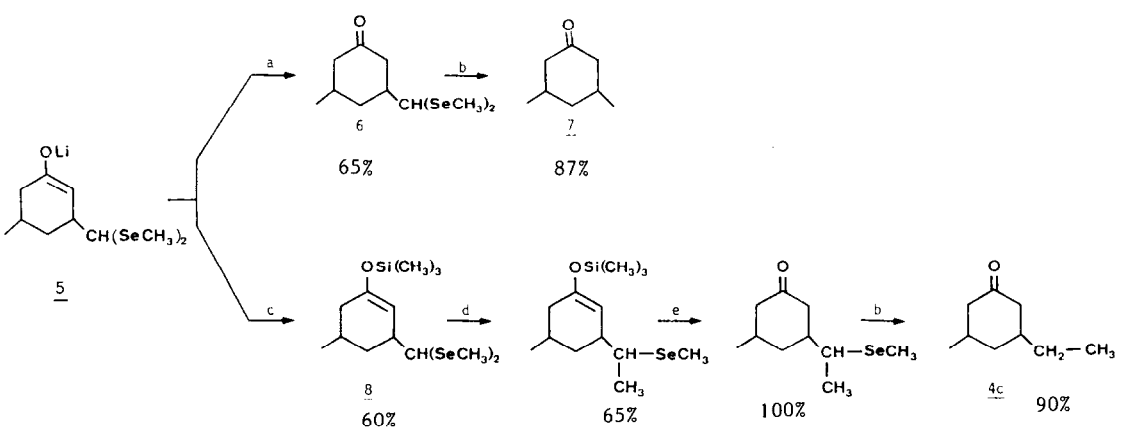


TABLE

Entry	R_1	E	Yields in 3 (Method)	Trans/cis Ratio Method A or B	Yields in 4	Trans/cis Ratio
1	H	CH_3	70 (A)*	3a'/3a" : 99/1	95	4a'/4a" : 99/1
2	2-CH_3	H	65 (A),51 (B)	3a'/3a" : 1/99	87	4a'/4a" : 1/99
3	3-CH_3	H	0 (A,B)	-	-	-
4	4-CH_3	H	58 (A),47 (B)	3b'/3b" : 95/5	74	4b'/4b" : 95/5
5	5-CH_3	H	76 (A),64 (B)	3c'/3c" : 87/13	90	4c'/4c" : 88/12
6	6-CH_3	H	74 (A),67 (B)	3d'/3d" : 32/68**	85	4d'/4d" : 32/68

* Then CH_3I-HMPT (5eq,5eq) in THF, 0°, 1hr. ** Each isomer can be obtained pure by preparative layer chromatography (SiO_2, ether/pentane 3/7 rf 0.62/0.57:3d'/3d") and have been reduced stereoselectively to the corresponding 4d.

SCHEME II



a. NH_4Cl/H_2O - b. Bu_3SnH,AIBN,Toluene,80°,0.2hr - c. $(CH_3)_3SiCl/Et_3N$ - d. n-BuLi 1eq,then CH_3I excess - e. 5% pTSOH/CH_3OH/H_2O.

References and notes

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5. 3-ethyl 2-methyl cyclohexanone 3a' is obtained in 25% yield when the reaction is performed with 1 eq instead of 5 eq of HMPT.

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11. We have also prepared 3-ethyl cyclohexanones 4 from various methylcyclohexenones 2 and ethyl magnesium bromide in ether containing catalytic amount of CuCl. This work will appear in the full paper.

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