Tetrahedron Letters Vol. 21, pp 1997 - 2000
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0040-4039/80/0502-1997$02.00/0

α-SELENOCYCLOBUTYLLITHIUM AS A 2-LITHIO-1,3-DIENE EQUIVALENT. REGIOSELECTIVE (100%) SYNTHESIS OF IPSENOL

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1-substituted cyclobutenes and 2-substituted dienes are prepared in high yield and regioselectively from a variety of electrophiles and cyclobutanone via α-lithio-α-seleno-cyclobutyllithiums.

1,3 Dienes are valuable synthetic intermediates[1], readily available from cyclobutenes by their thermal concerted ring opening.[2,3]

The regioselective synthesis of the latter is therefore a particularly valuable process.

We present in the letter our preliminary results in this field which take advantage of the ready availability of 1,1-bis (seleno) cyclobutanes from cyclobutanone[4] (RSeH, $ZnCl_2$ 0.5eq, CCl_4 - R:C_6H_5 84%, R:CH_3 89%); their quantitative cleavage[5] to the corresponding α-lithio selenocyclobutanes (nBuli/THF, -78°) which further allow the high yield synthesis of the corresponding selenides, β-hydroxy and γ-hydroxyselenides on reaction[5] with primary alkyl halides, carbonyl compounds and epoxides respectively.

The crucial step of this scheme (1 → 7) is the specific introduction of an intra- rather than extra-cyclic double bond in the four membered ring producing 5 by formal "H-SeR" elimination on 2.

Two distinct routes have been tested to achieve the synthesis of cyclobutenes 5 depending on the nature of the group E present in 2.

The first one takes advantage of the well known elimination on an *in situ* formed selenoxide 3 ($tBuOOH/Al_2O_3/THF$, 50°, 3 hours, Method A).[6]

This reaction is particularly valuable for the synthesis of cyclobutenyl alcohols 5 (scheme I entries a-c), the elimination of hydrogen taking place exclusively from the ring.

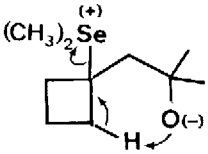
The method, however, is not suitable for 1-seleno-1-alkyl cyclobutanes 2 (scheme I entry d) and for γ-hydroxyselenides bearing an α-cyclobutyl group 2 (scheme I entry i) since in both cases the cyclobutylidene derivatives 6 are formed in appreciable amounts besides the desired cyclobutenes 5.

These cyclobutenes 5 (entries e,f-h) are indeed formed with a high degree of selectivity (93 to 100%) on reaction of the corresponding selenonium salts 4 (CH_3I/$AgBF_4$, CH_2Cl_2, 20°) with potassium tertiobutoxide in dimethylsulfoxide (20°, method B)[7] or with potassium hydride in the same solvent (20°, method C).

The selectivities just disclosed can be speculatively explained by a rapid isomerisation of a first formed 5+6 mixture, the position of equilibrium being known to lie far in favour of the cyclobutene[9].

In the case of γ-hydroxycyclobutenes 5 (entries f-h) the observed selectivity can also be attributed to a regiocontrolled intramolecular elimination reaction already proposed for open chain analogues[8] (scheme III).

Scheme III



The structure of the nonylidene cyclobutane 6 (scheme I entries d,e) has been proved by comparison with a sample regioselectively prepared from 1-cyclobutyl 1-seleno-2-hydroxynonane (PI_3/NEt_3/CH_2Cl_2, 20° or $(Im)_2$ C=O, Toluene, 110° - Scheme II)[5,10].

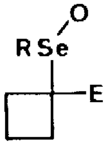
During the course of this study we also found that the methods B and C do not produce β hydroxycyclobutylselenides (scheme II) since, as already mentioned in the case of open chain analogues[11], an internal substitution reaction occurs on the intermediary β hydroxy selenonium salt 4 leading to an epoxide with high selectivity(100%) and high yield (see for example scheme II).

Finally we have achieved the synthesis of a variety of 2-alkyl dienes by thermal ring opening of the cyclobutenes[1,2] prepared by the routes just disclosed (scheme I).

The value of the synthetic scheme (1 → 7) is examplified by the regioselective synthesis of (±) Ipsenol 7 (entry h scheme I) one of the agregation pheromones of Ips bark beatles[3b,12] (paraconfusus Lanier) in more that 50% yield from cyclobutanone.

This synthetic scheme seems to apply to the synthesis of other natural terpenoids (eg: Tagetol) and may allow the formation of optically active (S)(-) Ipsenol from (S)(-) 1-oxido-4-methyl pentane[12]. Work towards this goal is in progress in our laboratory.

The authors acknowledge I.R.S.I.A. (Belgium) for the support of this research (fellowship to S.H.) as well as F.N.R.S. (Belgium) for financial support.



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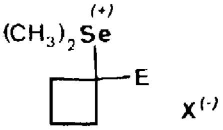

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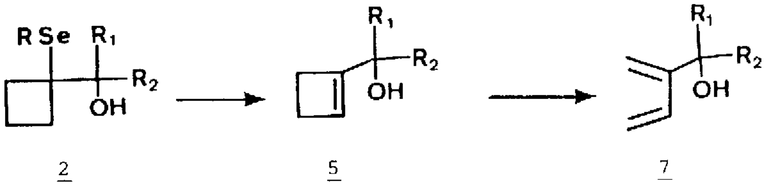
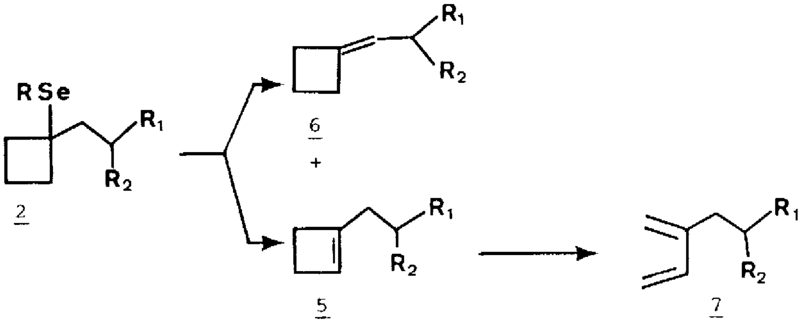
Scheme I

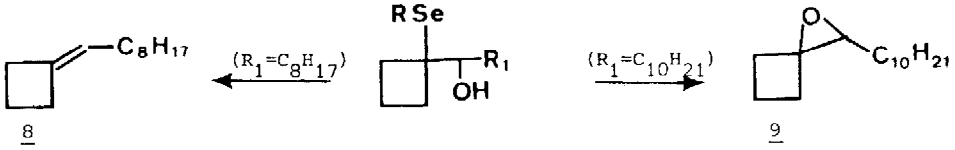


	R	R_1	R_2	Yield in $\underline{2}$%	Yield in $\underline{5}$%	Yield in $\underline{7}$%
a	C_6H_5	H	$C_{10}H_{21}$	71	70	75
b	C_6H_5	CH_3	C_9H_{19}	70	76	85
c	CH_3	H	$C_{10}H_{21}$	90	70	75



	R	R_1	R_2	Yield in $\underline{2}$%	Method	Yield in $\underline{6}$%	$\underline{5}$%	$\underline{7}$%
d	C_6H_5	H	C_7H_{15}	80	A	33	33	-
e	CH_3	H	C_7H_{15}	80	B	07	68	100
f	CH_3	OH	C_6H_{13}	72	B	00	60	100
g	CH_3	OH	$(CH_3)_2CHCH_2$	73	B	00	65	100
h	CH_3	OH	$(CH_3)_2CHCH_2$	73	C	00	77	100
i	CH_3	OH	$(CH_3)_2CHCH_2$	73	A	40	25	-

Scheme II



70% PI$_3$/NEt$_3$, 20° R : CH_3 1) CH_3I; 2) KOH 81% R = CH_3

91% $(Im)_2CO = O$, 110° R : C_6H_5

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(Received in UK 6 March 1980)