Pergamon

Tetrahedron Letters, Vol. 38, No. 46, pp. 8085-8088, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)10115-0

Synthesis of 1-Aryl-2-Vinyl Cyclopropanes by Intramolecular Carbolithiation

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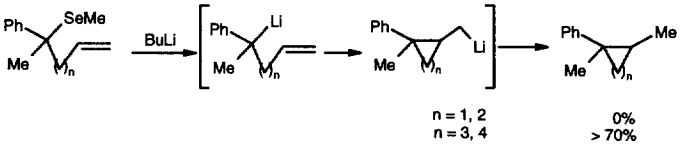
Abstract: Benzylselenides bearing a γ-alkenyl-ε-sulfonyloxy side chain react with butyllithiums to produce, via the corresponding benzyllithiums, 1-aryl-2-vinyl cyclopropanes.

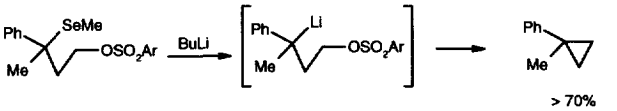
Some time ago, we disclosed that benzyllithiums have an exceptional propensity to add to unactivated C,C double bond especially if it is built in the molecule.[1] This reaction allowed the synthesis of 1-aryl-2-lithiomethyl cyclopentanes and cyclohexanes in high yield and with almost complete stereocontrol (Scheme 1).[1,2] It nevertheless could not be extended to the synthesis of related three or four membered cycles probably due to the strain involved. It is in fact known that the reaction works in the other direction and that lithiomethylcyclopropanes undergo ring fragmentation leading to the corresponding γ-alkenyllithiums.[3]

Scheme 1



We have been nevertheless able to synthesize 1-aryl cyclopropanes using a different approach which involves the reaction of γ-sulfonyloxy benzylselenides[4] with butyllithiums (Scheme 2), and which takes advantage of the unusually facile alkylation of the intermediate benzyllithiums.[5]

Scheme 2



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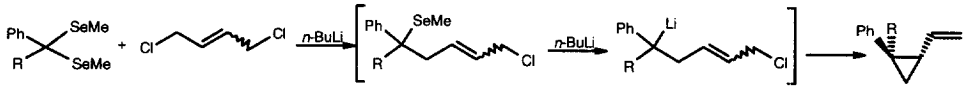
Dedicated to Prof. P. Welzel at the occasion of his 60 Birthday.

We now report that benzyl selenides **4** and **8**, bearing a γ-alkenyl-side chain and possessing a leaving group in ε-position, produce α-aryl-β-vinyl cyclopropanes **6** on reaction with butyllithium (Schemes 3, 4).

The most straightforward route to such compounds involves the addition of a mixture of 1,4-dichloro-but-2-ene **3** and the selenoacetal derived from benzaldehyde **1a** or acetophenone **1a'** onto a solution of *n*-butyllithium (1.6 M, 2 eq., THF-hexane, -78°C, Scheme 3). This reaction provides almost exclusively the *trans*-vinyl cyclopropane $\mathbf{6}_t$ in high yield from any of the stereoisomers of 1,4-dichloro-but-2-ene **3** (Scheme 3, compare entry a to b). The nature of the leaving group proved however to be crucial for success since the vinyl cyclopropane was not produced when 1,4-dibromo-but-2-ene is used place of the dichloride **3**.

Scheme 3



Entry	1	3	6	Yield in 6 % ($6_t/6_c$ ratio)
a	1a	3_E	6_t a	75 (96/4)
b	1a	3_Z	6_t a	89 (93/7)
c	1a'	3_E	6_t a'	68 (98/2)

This one pot reaction involves several steps which include :

(i) the formation of the α-methylselenobenzyllithium **2**, from the selenoacetal **1** and one of the equivalent of *n*-butyllithium and its trapping by 1,4-dichloro-but-2-ene **3** present in the medium,

(ii) cleavage of the C,Se bond of the resulting (α-aryl-ε-chloro)-γ-alkenyl selenide **4**[6] with the second equivalent of *n*-butyllithium which sequentially led to **5** and to **6**.

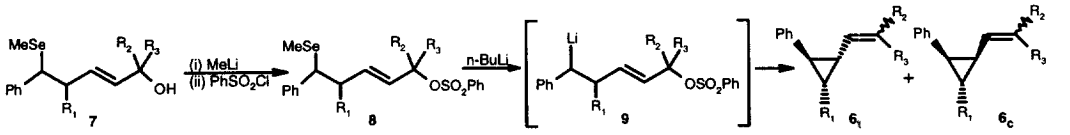
We have indeed proved that a competitive reaction, involving the chlorine/lithium exchange on **4** and further cyclisation to **6** by elimination of the methylseleno moiety is not operative since butyl methylselenide, resulting from the C/Se exchange both in **1** and **4**, is the only selenium by-product recovered. We have nevertheless no argument in favor of the mechanism (i) implying carbolithiation reaction followed by β-elimination of lithium chloride over (ii) an S_N2' reaction, which both are expected to produce the vinyl cyclopropane **6**. Anyhow, the elimination of the chlorine anion is crucial for the success of the cyclisation step since it draws the equilibrium towards the formation of the vinyl cyclopropane.[7]

We have successfully extended this reaction to α-phenyl-γ-alkenyl-δ-sulfonyloxy methylselenides **7** which are in fact vinylogous to the γ-sulfonyloxy benzylselenides shown in the Scheme 1.[5] The synthesis of the starting material required multi-step reactions (Scheme 5, 6) which contrast with the straightforward synthesis described in Scheme 1.

Typically the (*E*)-sulfonates, obtained from (*E*)-α-phenyl-γ-alken-δ-ols and benzenesulfonyl chloride ((i) 1eq. MeLi-ether, -78°C, THF (ii)1.8 eq. $PhSO_2Cl$, 0°, 1h) [9] have been reacted *in situ* with an excess of *n*-BuLi (1.8 eq, THF, -78°, 0.3h) to produce, in variable yields, the cyclopropane derivatives **6** as a mixture of

stereoisomers (Scheme 4). The yields are particularly good with those compounds bearing a primary benzene sulfonate moiety (Scheme 4, entries a,d) and modest to poor by increasing the substitution there (Scheme 4, entries b,d). The case of tertiary mesylate merits further comments since 2-methyl-6-phenyl-hexa-1,3-diene, resulting from a competitive elimination reaction on **9c**, is concomitantly formed besides several unidentified products. The *trans*-stereoisomer is mainly produced from ε-sulfonyloxyalkyl selenides **8** unsubstituted at C-β (Scheme 4, entries a-c) whereas the *cis*-stereoisomer prevails when a methyl substituent is attached there (Scheme 4, entry d). Apparently, in the later case, the interaction between the phenyl and the methyl group in the transition state leading to the cyclopropane derivative favors the epimerisation reaction at the benzylic site and permits, although the reaction has been carried out on a 67/33 mixture of diastereoisomers **7d** at C-α,C-β, this stereocontrol.[4,8] Finally, the (*E*)-stereoisomer $\mathbf{6b}_t$ is the major one from **7b** (*E*/*Z* = 9/1, Scheme 4, entry b).

Scheme 4

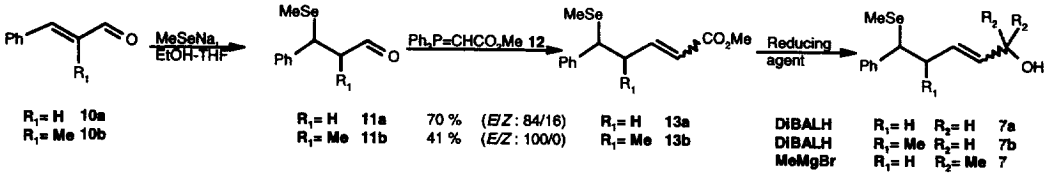


Entry	7	R_1	R_2	R_3	6	Yield in 6 % (6_t/6_c ratio)
a	**7a**	H	H	H	$\mathbf{6}_t$**a**	60 (85/15)
b	**7b**	H	Me	H	$\mathbf{6}_t$**b**	47 (83/17)
c	**7c**	H	Me	Me	$\mathbf{6}_t$**c**	28 (76/24)
d	**7d**	Me	H	H	$\mathbf{6}_c$**d**	85 (20/80)

The nature of the leaving group has also been briefly varied. We expected that this could provide interesting informations on the intimate mechanism of the reaction. The presence of an alkoxy group there could for example, favor the carbolithiation reaction by complexation of the lithium cation and act as a leaving group in the subsequent elimination reaction leading to **6**. We have, for that purpose, reacted n-butyllithium with a series of to α-phenyl-γ-alkenyl-methylselenides bearing in ε-position a lithiumalkoxy (OLi), an ester (Opiv) , an ether (OPh), a silyl ether (OTBDMS) and a thioether (SPh) group.[10] The cyclisation was only successful on the selenide bearing a phenoxy (OPh) group in ε-position and provides, upon warming at - 50°C, $\mathbf{6}_t$**a** in modest yield (26 %, e.d. : 62 %). Work is in progress to delineate the scope of this reaction.

Compounds **7a-c**, required for this work, have been synthesized from cinnamaldehydes **10** by the set of reactions disclosed in Scheme 5. Sequential reactions of **10a-b** with sodium methylselenolate (3.5 eq., EtOH-THF, 20°C, 0.1 h) then with the ylide **12** (Benzene, 20°C, 12 h) produce the α,β-unsaturated esters **13** as mixture of stereoisomers (**13a** : 70 % yield (E/*Z*= 84/16) ; **13b** : 41 % yield (*E*/*Z*= 100/0, d.e. 34)). These esters have been easily separated by column chromatography on SiO_2 and have been regioselectively reduced to the alcohols **7a,b** on reaction with DIBALH (2 eq., toluene, -78°C, 0.5 h, $\mathbf{7a}_Z$: 72 % yield ; $\mathbf{7a}_E$: 95 % yield; $\mathbf{7b}_E$: 78 % yield (d.e. : 34)) and to **7c** on reaction with methyl magnesium bromide (THF, 20°C, 3 h, 84 % yield).

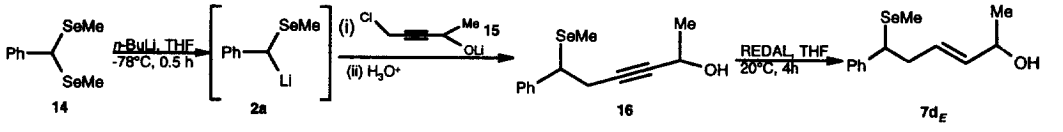
Scheme 5



Alternatively the (*E*)-allyl alcohol **7d**$_E$ was synthesized in a straightforward manner by reduction of the alkynol **16** (d.e.: 80) with REDAL (1 eq., THF, 20°C, 1 h, 50% yield (d.e.: 80)).

The alkynol **16** has been in turn prepared from corresponding selenoacetal **14** by sequential cleavage of its C,Se bond with *n*-butyllithium ((i) 1.2 eq. *n*-BuLi, THF, -78°C, 0.5 h) followed by alkylation of the resulting α-selenobenzyllithium **2a** with the propargylic chloride **15** (1 eq., THF, -78°C, 0.5 h then H_3O^+, 70% yield).

Scheme 6



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6. We have been able to isolate **4** , albeit in low yield, on carrying out the reaction of **1a** and **3** with only one equivalent of *n*-BuLi. We have not observed its regioisomer, resulting from an S_N2' alkylation of **3**.
7. For other examples of intramolecular carbolithiation-elimination see: (a) Broka, C. A.; Shen, T. *J. Am. Chem. Soc.* **1989**, *111*, 2981-84 (b) Bailey, W. F.; Zarcone, L. M. *Tetrahedron Lett.* **1991**, *32*, 4425-26 (c) Manabe, S.; *Chem. Commun.* **1997**, *8*, 737-38.
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9. We have not been able to produce the (*Z*)-sulfonates since they decompose very rapidly. This is probably due to an intramolecular substitution of the sulfonate by the selenide placed in suitable position owing to the stereochemistry of the C,C double bond.
10. The synthesis of these compounds will be reported in the full paper.

(*Received in UK* 18 *July* 1997; *revised* 11 *September* 1997; *accepted* 12 *September* 1997)