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Synthesis of Optically Pure Trisubstituted Ethynyloxiranes by Oxirane Deprotonation

D. Grandjean, P. Pale*, J. Chuche

Laboratoire de Chimie Organique Physique, associé au CNRS, Université de Reims-Champagne-Ardenne,
BP 347, 51100 Reims, France.

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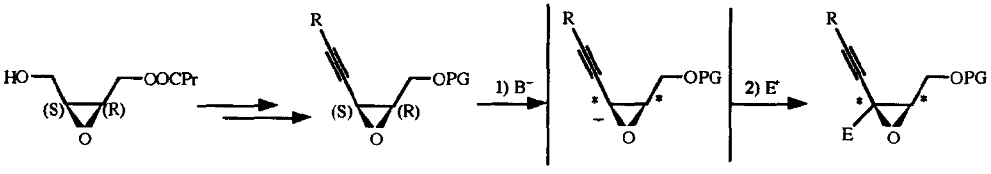
Abstract: Optically pure ethynyloxiranes were easily deprotonated by nBuLi and the corresponding anions trapped by various electrophiles, providing a stereocontrolled access to optically pure trisubstituted ethynyloxiranes.

Oxiranyl anions[1] are quite unstable species.[2] However, when oxiranes bear electronwithdrawing substituents[3-6] or heteroaromatic[7], aromatic or unsaturated groups,[8] the corresponding oxiranyl anions become stable enough to be trapped by electrophiles (Scheme 1).[9] Despite this increasing interest for such a chemistry, synthetic applications of oxiranyl anions are still scarce.

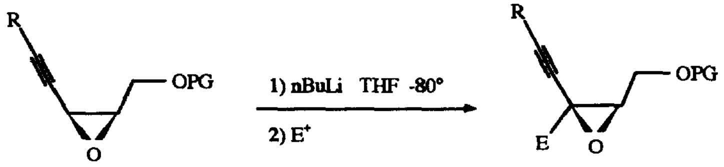
Due to our interest in the chemistry of ethynyl oxiranes, and in connection with the synthesis of various natural products,[10-11] we decided to develop a stereoselective access to trisubstituted chiral oxiranes bearing an ethynyl substituent based on the oxiranyl anion methodology (Scheme 1). We recently reported a convenient access to optically pure *cis*-epoxyalcohols based on enzymatic hydrolysis of *cis*-1,4-bis(butyryloxy)-2,3-epoxybutane.[12] The (2*S*, 3*R*)-4-butyryloxy-2,3-epoxybutan-1-ol so obtained is a suitable enantiomerically pure starting material for the asymmetric synthesis of ethynyl oxiranes.[13] This and the fact that oxyranyl anions usually[14] do not epimerize during the deprotonation and alkylation steps, led us to envisage the formation of oxiranyl anions as a tool for the stereoselective synthesis of trisubstituted optically pure ethynyl oxiranes (Scheme 1).



Scheme 1

To the best of our knowledge, a single case of successful deprotonation and trapping of an ethynyl oxirane was recently mentionned within the extensive work of Eisch and coll.,[9] on the deprotonation of α-unsaturated oxiranes. In the literature, none of the reported cases of oxiranyl anion trapping referred to optically active oxiranes.

In this communication, we present our preliminary results showing that various optically pure ethynyloxiranes can easily be deprotonated and the resulting oxiranyl anions selectively trapped at the oxiranyl position by electrophiles. Our results are collected in Table 1.



PG = protective group E = electrophile

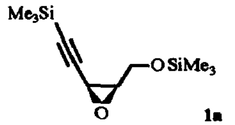
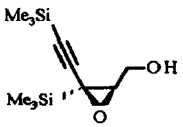
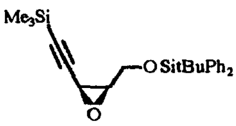
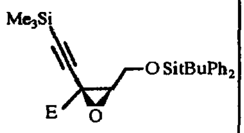
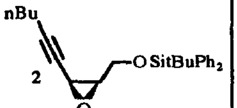
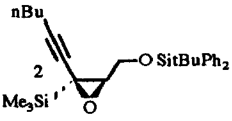
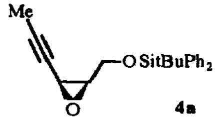
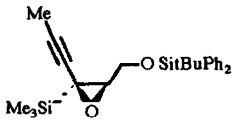
	Ethynyl oxiranes	Electrophile	Solvents	Yield[a]	Conv.	Trisubstituted oxiranes
1	 **1a**	Me_3SiCl	THF	94 %	100 %	 **1b**
2	 **2a**	Me_3SiCl	THF	96 %	100 %	E = Me_3Si **2b** 
3		MeI	THF	81 %	100 %	E = Me **2c**
4		$nC_6H_{13}CHO$	THF	97 %[b]	93 %	E = $nC_6H_{15}\underset{OH}{C}H$ **2d**
5		$MeSO_2Cl$	THF	0 %	0 %	E = — —
6	 **3a**	Me_3SiCl	THF	98 %	100 %	 **3b**
7	 **4a**	Me_3SiCl	THF	35 %[c]	100 %	 **4b**

Table 1: a) yields of isolated product; b) yield calculated from conversion; c) several non-identified by-products were also formed.

In order to determine suitable conditions, optically pure **1a** was prepared[13] as a model and deprotonated at -78°. Although strong or complex bases are usually required,[4-5] we found nButyl lithium basic enough to easily abstract the propargylic proton of **1a**. The anion derived from **1a** proved to be relatively stable at low temperature. With trimethylsilyl chloride as an electrophile, quenching of the anion was essentially quantitative, but the product was isolated as the free alcohol **1b**, $[\alpha]_D^{22} = +8.2$.[15] (Table 1, entry 1). Although the starting material was optically pure and no racemisation could occur in this reaction, the optical purity of **2b** was checked by ^1H NMR in the presence of chiral shift reagent ($Eu(hfc)_3$) after conversion to its acetate. A single set of signals was observed in the conditions where the racemic compound displayed two sets.

The oxiranyl anion derived from the *tert*butyldiphenylsilyl analog **2a** was quenched with representative electrophiles. In tetrahydrofuran, the expected products, resulting from silylation (Table 1, entry 2) or alkylation (Table 1, entries 3-4) at the propargylic carbon of the three membered ring, was isolated in good to excellent yield. As in the case of **1a**, quenching of the anion with trimethylsilyl chloride quantitatively led to the trissilylated compound **2b**, $[\alpha]_D^{22} = +4.5$,[15] (Table 1, entry 2). Methyl iodide efficiently reacted in pure tetrahydrofuran with the anion derived from **2a** to give the expected product **2c** in good yield (Table 1, entry 3) together with some minor by-products. **2c** proved to be spectroscopically identical to a sample independently prepared from the commercially available (*Z*)-3-methylpent-2-en-4-yn-1-ol. This demonstrated the complete stereochemical stability of the oxiranyl anion derived from **2a** in the conditions described here. Heptanal cleanly reacted in pure THF with the anion derived from **2a** (Table 1, entry 4). The expected epoxy alcohol was almost quantitatively formed but without any significative diastereoselection (1 - 1.3 mixture of diastereoisomers), in agreement with previous related work.[6]

As a rapid access to a class of natural products,[16] direct sulfonylation of the ethynyl oxirane anion was also attempted using **2a** as starting ethynyl oxirane. However, none of the expected product was formed. In the conditions we used, only extensive degradation was observed (Table 1, entry 5).

Ethynyloxiranes bearing at the ethynyl end of the molecule an other substituent than the trimethylsilyl group could also be deprotonated by nButyl lithium. As an exemple in the naturally occuring polyyne class of ethynyloxiranes,[16] the compound **3a**,[11] bearing an 1'-hexynyl chain, was submitted to deprotonation. After trapping with trimethylsilyl chloride, **3a** yielded almost quantitatively the expected trimethylsilyl substituted oxirane **3b**, $[\alpha]_D^{22} = -1.8$,[15] (Table 1, entry 6). However, the analog **4a** bearing the simplest alkyl group, *i. e.* a methyl substituent, gave a complex mixture from which the expected product **4b**, $[\alpha]_D^{22} = -2.7$,[15] was isolated in rather modest yield (Table 1, entry 7).

In summary, we have shown that ethynyl stabilized oxiranyl anions can be easily generated using the convenient nButyl lithium base. Reactions of these ethynyl oxiranions with various electrophiles stereospecifically led to trisubstituted oxiranes. Optically pure trisubstituted ethynyl oxiranes have easily been obtained from the corresponding optically pure *cis* disubstituted ethynyl oxiranes

Due to the availability of oxiranes,[17] especially in an optically active form,[12, 18] this deprotonation and alkylation sequence provides an efficient and stereocontrolled access to trisubstituted functionnalized oxiranes. Further developments as well as synthetic applications are now under current investigations in our laboratory and will be reported in due course.

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References and Notes

1) "oxiranyl anions" or "oxiranions" refered to organometallics derived from oxirane ring, regardless of
its exact nature.

2) Oxiranyl anions usually rearrange to α-alkoxy carbenes even at low temperature; see:
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14) It seems that considerable strain can facilitate isomerization of oxiranyl anion; see ref.6.
However, it has been observed that sulfonyl oxiranion suffered from partial isomerization
see: *J. Chem. Soc., Perkin Trans. I*, **1991**, 897.

15) optical rotations were determined in methylene chloride at the following concentrations:
1b, C = 0.43; 2b, C = 0.54; 3b, C = 0.22; 4b, C = 0.12.
All knew compounds were fully characterized by ^{1}H and ^{13}C NMR, IR, MS spectroscopies and when possible by elemental analysis.

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