Pergamon

Tetrahedron Letters 39 (1998) 8837–8840

TETRAHEDRON
LETTERS

A Stereospecific Synthesis of Bromoallenols from Propargylic Epoxides.

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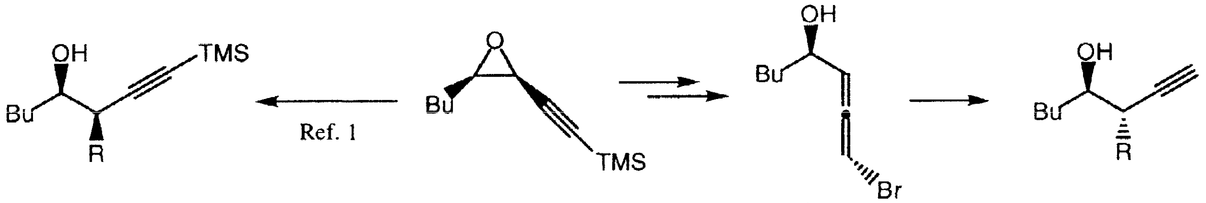
Received 8 July 1998; accepted 17 September 1998

Abstract : The stereospecific preparation of syn or anti bromoallenols from propargylic epoxides is described.

We have recently disclosed a stereospecific synthesis of homopropargylic alcohols[1], and we were interested in developing an alternative approach : we have shown that from the propargylic epoxide **1**, the disubstituted *syn* homopropargylic alcohol **3**-*syn* can be prepared by the BF_3-mediated direct opening with pure inversion of configuration at the propargylic carbon atom[1]. We thought that an overall retention of configuration could be achieved by double S_N2' inversion via the preparation of the bromoallenol **2**, leading to the disubstituted *anti* homopropargylic alcohol **3**-*anti*, as depicted on the following scheme (Scheme 1) :



3-*syn* **1** **2** **3**-*anti*

Scheme 1

The synthesis of bromoallenes[2] has been achieved in a stereospecific fashion generally starting from acetylenic sulfonates[3-5] (tosylates, mesylates or triflates) or alcohols[6-8]. We thought that epoxides as good leaving groups should behave like sulfonates. However no formation of the desired product was observed in the conditions described by Goré[3] (CuBr-LiBr in THF), either at low temperature, room temperature or even in refluxing THF, with stoichiometric quantities or with excess of salts. Only the decomposition of the starting material was observed. Addition of magnesium bromide as Lewis acid or replacement of copper bromide by the soluble complex CuBr-Me_2S gave the same result.

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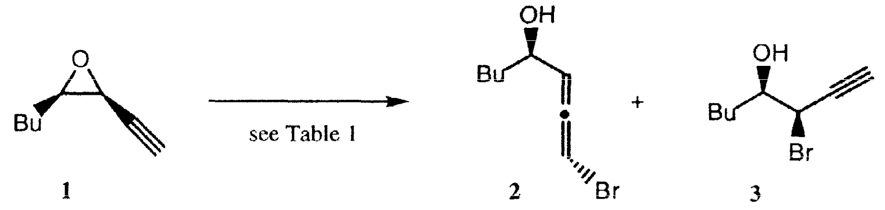
PII: S0040-4039(98)01981-9

We then turned to the conditions described by Landor in the case of propargylic alcohols. In the course of our attempts, two products could be obtained : the bromoallenol **2** and the bromohydrin **3** (Scheme 2). The results are summarized in the Table 1 :



Scheme 2

Table 1. Bromoallenol **2** *vs* Bromhydrin **3** from Propargylic Epoxide **1**.

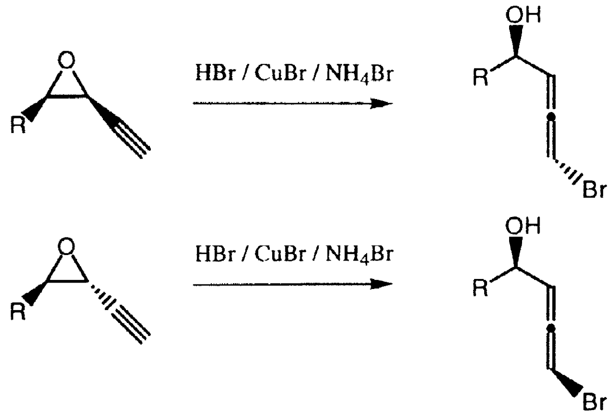
Entry	Conditions	Yield of **2**	Yield of **3**
1	HBr, H_2O	0	70
2	HBr (3 eq.), CuBr (2 eq.), H_2O	30	40
3	HBr (1 eq.), CuBr (1 eq.), H_2O	40	40
4	HBr (1 eq.), CuBr (1 eq.), H_2O, then NaOH*	50	0
5	HBr (1 eq.), CuBr (1 eq.), NH_4Br (0.5 eq.), H_2O	70	0

* The reaction was repeated three times under these conditions.

As can be seen on the Table 1, the use of concentrated hydrobromic acid gave only the bromohydrin **3** (entry 1), whereas the use of Landor's conditions[6] (entry 2 and 3) gave mixtures of bromohydrin and bromoallene nearly in a 1:1 ratio. We found that the bromohydrin can be easily converted into starting epoxide **1** by a simple treatment with 10% sodium hydroxide in water. Under these conditions the bromoallene **2** remains unchanged. Exposure of the resulting mixture of **1** and **2** to the same conditions gave again the bromohydrin, albeit in lower proportion, admixed with the bromoallene. Finally we could obtain a reasonable yield of **2** by repeating three times these operations (entry 4).

However, the use of NH_4Br, as also described by Landor (for propargylic alcohols)[7], avoided these tedious operations. In the presence of HBr (1 eq.), CuBr (1eq.) and NH_4Br (0.5 eq.), the starting epoxide was converted into bromoallene in a good yield (entry 5) and in a stereospecific manner[9].

This method can also be applied to other propargylic epoxides, again with an excellent diastereocontrol: *syn* epoxides lead to *anti* bromoallenols, whereas *anti* epoxides give *syn* bromoallenols, as depicted on the scheme 3 :

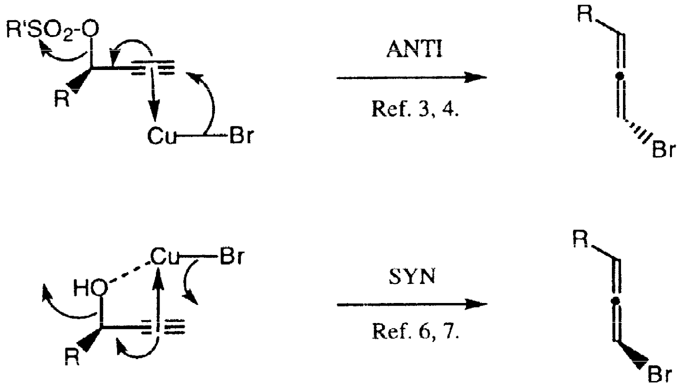


R = Bu : 70 %
R = i-Pr : 55 %

R = Bu : 65 %
R = i-Pr : 73 %

Scheme 3

Whereas the transformation of propargylic sulfonates into bromoallenes is known to follow an *anti* S_N2' mechanism[4], the conversion of propargylic alcohols is thought to follow a *syn* S_N2' mechanism[7], as depicted in the scheme 4. The difference is attributed to the presence of a Cu-O chelation :



Goré's conditions : CuBr / LiBr / THF

Landor's conditions : CuBr / HBr / H_2O

Scheme 4

In our case, the configuration was unambiguously attributed as *anti* by the transformation of the bromoallenol with an organocuprate into a disubstituted homopropargylic alcohol of known stereochemistry (see the following paper). Although the presence of a proton source is necessary to the reaction, as was the case for alcohols, the copper species seems not to be complexed to the oxygen, presumably due to stereoelectronic effects, and then epoxides behave like sulfonates on a stereochemical point of view.

In conclusion we have disclosed a new and highly stereospecific synthesis of *syn* or *anti* disubstituted bromoallenols starting from propargylic epoxides. Further results in this field will be reported in due course.

Acknowledgments : Thanks are due to M. Baudry for the preparation of starting materials and to Pr. A. Alexakis for many helpful discussions.

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9. Experimental procedure : A mixture of HBr (1.2mL of a 47% aqueous solution), CuBr (10mmol, 1.44g), NH_4Br (5mmol, 0.490g) was added at -5°C to a solution of the propargylic oxirane (10 mmol) in Et_2O (1mL). The mixture was stirred at -5°C, the reaction was followed by GC. The solution was quenched with an aqueous solution of NH_4Cl/NH_3, extracted twice with Et_2O (20 mL); the combined organic layers were washed with brine, dried over Na_2SO_4, and the solvent removed *in vacuo*; the obtained bromoallene was purified by column chromatography on silica gel using cyclohexane : ethyl acetate (90 : 10) as eluent.