Pergamon

Tetrahedron Letters 40 (1999) 75–78

TETRAHEDRON
LETTERS

Metalation of 3-Trimethylsilyl Propargyl Chloride : A Stereoselective Access to *trans*-Propargylic Oxiranes.

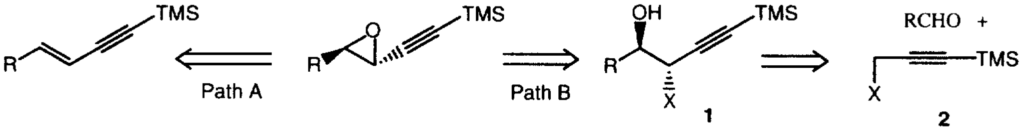
Fabrice Chemla*, Nicolas Bernard and Jean F. Normant

Laboratoire de Chimie des Organo-Eléments, associé au CNRS, Université Pierre et Marie Curie,
4, Place Jussieu, Tour 44-45, 2^e étage, Boîte 183, 75252 Paris Cedex 05, France

Received 21 October 1998; accepted 3 November 1998

Abstract : The metalation of 3-trimethylsilyl-1-chloroprop-2-yne and the subsequent reaction with aldehydes affords stereospecifically *anti*-chlorohydrins which give after treatment with potassium fluoride and NaOH propargylic epoxides with good to excellent yields. © 1998 Elsevier Science Ltd. All rights reserved.

In the course of our studies towards the preparation of 1,2-disubstituted homopropargylic alcohols[1,2], we were in need of a rapid preparation of propargylic epoxides on a large scale. These epoxides are currently prepared by oxidation of the corresponding enynes with MCPBA[3] or oxone®[4]; however, these enynes have then to be prepared, generally by a coupling reaction[5] (path A). We have planned an alternative strategy, based on the possible stereoselective formation of a propargylic halohydrin 1 and its subsequent ring-closure (path B) :



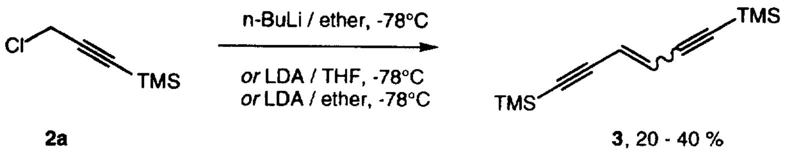
To the best of our knowledge, no direct preparation of this type of halohydrin has been described. Brandsma has reported a simple preparation of trimethylsilyl propargyl chloride (X = Cl, **2a**) and bromide (X = Br, **2b**)[6]; however, although he mentioned the possibility of metalation, nothing has been published concerning this topic[7].

Our first trials to deprotonate the compound **2a** were unsuccesful : in all conditions we used, we obtained only the self-condensation product **3** in low yields. This reaction has already been reported on substituted propargyl bromides[8] :

---

* FAX : 00 33 - 1 44 27 75 67 ; Email : fchemla@ccr.jussieu.fr

PII: S0040-4039(98)02374-0



This reaction occurs certainly because the deprotonation reaction is slower than the substitution; we then tried to quench the formed carbanion by transmetalation as it was formed. We were pleased to see that when the metalation was conducted *in the presence of zinc bromide*, no more self-condensation was observed[9]. The resulting zinc carbenoid could then react with aldehydes or ketones to give the corresponding chlorohydrins **1a-g**. Less than 2% (by ^1H NMR spectrometry) bromoallene was found, indicating then the presumable intermediacy of the zincioallene **4**[10]. Our results are reported on Table 1 :

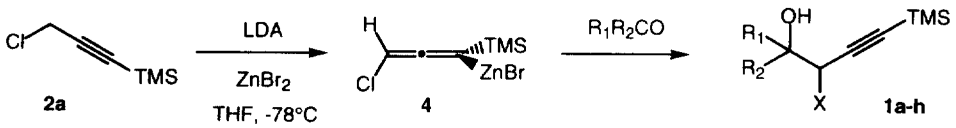
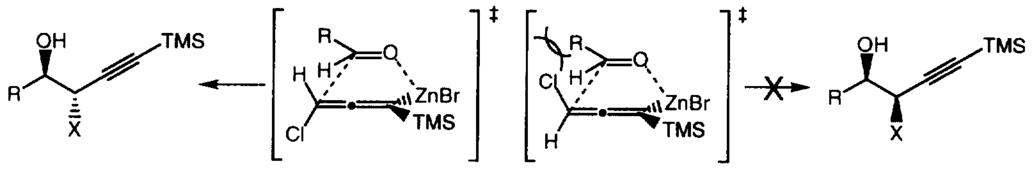


Table 1. Reaction of zincioallene **4** with carbonyl electrophiles.

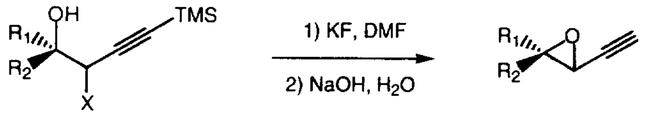
Entry	Electrophile	Chlorohydrin	Yield (%)	*anti / syn*
1	n-BuCHO	**1a**	81	85 / 15
2	i-PrCHO	**1b**	75	95 / 5
3	t-BuCHO	**1c**	82	100 / 0
4	PhCHO	**1d**	75	62 / 38
5	4-MeOPhCHO	**1e**	81	60 / 40
6	*(E)*-Cinnamaldehyde	**1f**	75	80 / 20
7	Cyclohexanone	**1g**	70	
8	Methylvinylketone	**1h**	91	50 / 50

As it can be seen in Table 1, the diastereomeric ratio seems to be very dependent on the steric hindrance of the aldehyde (entries 1,2,3 and 6) or ketone (entry 8). This good stereoselectivity can be attributed to a transition state TS-1, leading then to the major *anti* diastereoisomer, whereas the other possible transition state TS-2 reveals some steric interactions (Scheme 3). For aromatic aldehydes, the diastereomeric excess is lower; the reasons remain unclear, but this has found many precedents in the literature[10]. However, the use of trimethylsilyl propargyl *bromide* in the same conditions *did not* enhance the diastereomeric control : the corresponding bromohydrins were obtained in almost the same diastereomeric excess, albeit in lower yields, due to the more important formation of coupling products **3**.



1 *anti* TS-1 TS-2 **1** *syn*

Having in hand a good and easy access to chlorohydrins, we then turned to the ring closure of these compounds to obtain the corresponding epoxides. We were particularly interested in a method which could lead us to the epoxides either *with*[1] or *without*[2] the trimethylsilyl group. The ring closure *with* desilylation was easy to optimize : a classical desilylation with KF in DMF, followed by a simple treatment by a 10% NaOH aqueous solution, gave the corresponding epoxides 5d-g in good yields. Our results are reported in Table 2.



1d-g **5d-g**

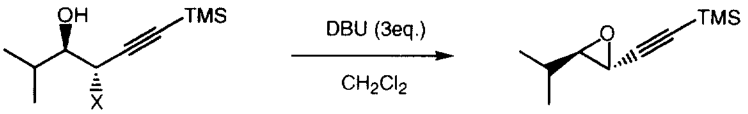
Table 2. Formation of desilylated epoxides **5** from chlorohydrins **1**.

Entry	Chlorohydrin	Epoxide	Yield (%)
1	**1d**	**5d**	95
2	**1e**	**5e**	97
3	**1f**	**5f**	90
4	**1g**	**5g**	74

As it can be seen in the table, some desilylated epoxides (starting from chlorohydrins **1a-c** and **1h**) could not be obtained, owing to their low boiling point. The ring closure is stereoselective as the *cis/trans* ratio was directly related to the *syn/anti* ratio of the starting chlorohydrin[11].

Moreover, the epoxides *cis* and *trans* were found to be easily separable by flash-chromatography over silicagel. This is also important as these epoxides can be used to the preparation of 1,2-disubstituted homopropargylic alcohols, either with inversion[1] or with retention[2] of the configuration at the propargylic carbon atom.

The ring closure *without* desilylation was surprizingly very difficult to manage. Most protic conditions (aqueous NaOH, aqueous KOH) or aprotic conditions (MeLi/ether, NaH/ether or THF, Et_3N/ether) gave us the starting material or decomposition products. Finally, we found that a treatment with three equivalents of DBU in dichloromethane lead smoothly to the correspondingtrimethylsilyl epoxides in high yield :



1b

6, 97 %

This way is currently under investigation. Further results will be reported in due course.

Acknowledgments : Thanks are due to M. Baudry for the preparation of starting materials.

References

1. Bernard, N.; Chemla, F.; Normant, N. *Tetrahedron Lett.* **1998**, *39*, 6715.
2. Bernard, N.; Chemla, F.; Normant, N. *Tetrahedron Lett.* **1998**, *39*, under press.
3. See for example : Carlson, R.G.; Cox, W.W. *J. Org. Chem.* **1977**, *42*, 2382; Alexakis, A.; Marek, I.; Mangeney, P.; Normant, J.F. *Tetrahedron* **1991**, *47*, 1677-1696.
4. Cao, G.-A.; Wang, Z.X.; Tu, Y.; Shi, Y. *Tetrahedron Lett.* **1998**, *39*, 4425 and ref. cited therein.
5. Sonogashira, K. Coupling Reactions Between sp^2 and sp Carbon Centers, in: *Comprehensive Organic Synthesis*, Trost, B.M.; Fleming, I. eds. ; Pergamon Press: London, 1991; *3*, pp 521-549.
6. Verkruijsse, H.D.; Brandsma, L. *Synth. Commun.* **1990**, *20*, 3375; for an alternate preparation, see : Komarov, N.N.; Shostakovskii, M.F.; Astaf'eva, L.N. *J. Gen. Chem. USSR* **1961**, 1963.
7. For related preparation of epoxides and aziridines through condensation of propargylic ylides onto aldehydes or imines, see: Zhou, Z.L.; Huang, Y.Z.; Shi, L.L.; Hu, J. *J. Org. Chem.* **1992**, *57*, 6598; Li, A.H.; Zhou, Y.G.; Dai, L.X.; Hou, X.L.; Xia, L.J.; Lin, L. *J. Org. Chem.* **1998**, *63*, 4338.
8. Huber, R.S.; Jones, G.B. *Tetrahedron Lett* **1994**, *35*, 2655; Jones, G.B.; Huber, R.S.; Mathews, J.E. *J. Chem. Soc., Chem. Commun.* **1995**, 1791; McPhee, M.M.; Kerwin, S.M. *J. Org. Chem.* **1996**, *61*, 9385.
9. The same phenomenon has already been reported in the case of chloroallyl anions : Mallaiah, K.; Satyanarayana, J.; Ila, H.; Junjappa, H. *Tetrahedron Lett.* **1993**, *34*, 3145.
10. Epzstein, R. The Formation and Transformations of Allenic and α-acetylenic Carbanions, in: *Comprehensive Carbanion Chemistry*, Buncel, E; Durst, T. eds ; Elsevier: Amsterdam, 1984; B, pp 107-175; Yamamoto, H. Propargyl and Allenyl Organometallics, in: *Comprehensive Organic Synthesis*, Trost, B.M., Fleming, I. eds. ; Pergamon Press: London, 1991; 2, pp 81-98.
11. For a related example of ring-closure of propargylic bromohydrins, see :Kanger, T.; Niidas, P.; Müürisepp, A.; Pekh, T.; Lopp, M. *Tetrahedron: Assym.* **1998**, *9*, 2499.