Tetrahedron Letters, Vol. 34, No. 8, pp. 1363-1366, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

Lithiation of Benzothiazolyl Substituted Epoxides and Reactions with Electrophiles.

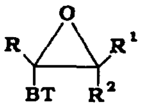
S. Florio,*[a] G. Ingrosso,[b] L. Troisi,[b] V. Lucchini [c]

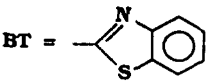
a) Dip. Farmaco-Chimico, Università di Bari, Traversa 200 Re David, 4, 70125 Bari, Italy.
b) Dip. di Biologia, Università di Lecce, Via Monteroni, 73100 Lecce, Italy.
c) Dip. Scienze Ambientali, Università di Venezia, Via Dorsoduro 2137, 30123 Venezia, Italy.

Abstract: Deprotonation of epoxides **1** with n-BuLi or LDA at -90°C produces dark red solutions of oxiranyllithiums **2** which react with electrophiles leading to oxiranes **3**.

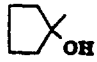
Due to their enhanced reactivity mainly attributable to a high degree of ring strain, epoxides represent a versatile class of extremely useful synthetic intermediates.[1] Among the many routes to epoxides now available, one method that has yet to be fully developed is the coupling reaction of oxiranyl anions with electrophiles.[2] Some oxiranyllithiums have been reported to offer good chance for the functionalization of epoxides. The generation of such organolithiums by lithiation of the corresponding epoxides is made possible by the presence on the epoxide ring of suitable substituents such as heteroatoms or unsaturated organyl groups, capable of stabilizing the carbanionic species.[3] Unstabilized oxiranyllithiums are rather prone to α-elimination.[3] Lithiation of unstabilized epoxides has been recently made possible by tin-lithium exchange of the organotin precursors.[4]

Heteroaryl substituted oxiranyllithiums have never been described so far. We report in the present communication on the lithiation of 2-benzothiazolyl substituted epoxides **1**[5,6] and reactions of the resulting oxiranyllithiums **2**.



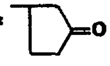


1a: R=H; $R^1=R^2=Me$
1b: $R=R^1=H$; $R^2=Me$
1c: $R^1=Me$; $R=R^2=H$
1d: $R=R^1=R^2=Me$
2a: R=Li; $R^1=R^2=Me$
2b: R=Li; $R^1=H$; $R^2=Me$
2c: R=Li; $R^1=Me$; $R^2=H$

3a: $R^1=R^2=Me$; $R=Me_3SiCl$
3b: $R^1=R^2=Me$; R= 

3c: $R^1=R^2=Me$; R=PhCHOH
3d: $R^1=R^2=Me$; $R=2,6\text{-}Cl_2C_6H_3CHOH$
3e: $R^1=R^2=Me$; $R=CH_3CHOH$
3f : $R^1=H$; $R^2=Me$; R=PhCHOH

3g: $R^1=R^2=Me$; R= 

3h: $R^1=R^2=Me$; R= 

Upon treatment with **n**-BuLi in THF at -90°C the oxirane **1a** underwent rapid lithiation which was complete in less than 10 min to generate **2a**.[7] The formation of **2a** was proved by trapping it with Me_3SiCl to give trimethylsilyl derivative **3a** and by methylation with MeI to give **1d**. **2a** tends to convert into benzothiazolyl isopropyl ketone upon warming to room temperature likely through an eliminative ring fission.

Treatment of epoxide **1a** with **n**-BuLi followed by a quench with cyclopentanone afforded a good yield of epoxy alcohol **3b**, while the coupling of **2a** with benzaldehyde furnished the coupled product **3c** (syn and anti). Comparable result was obtained when **2a** was prepared by lithiation of **1a** with lithium diisopropylamide(LDA). In both cases the coupling reaction proceeded with good anti diastereoselectivity, as ascertained by single-crystal X-Ray diffractometry of the major isomer of **3c** showing the R,R configuration at the C_8 and C_9 carbon atoms (Figure 1). Similarly, the reaction of **2a** with 2,6-dichlorobenzaldehyde and acetaldehyde afforded a mixture of the syn and anti diastereomers **3d** and **3e** respectively. Moreover, the reaction of **2a** with 2-cyclopenten-1-one gave a mixture of 1,2- and 1,4-addition products **3g** and **3h** (Table).

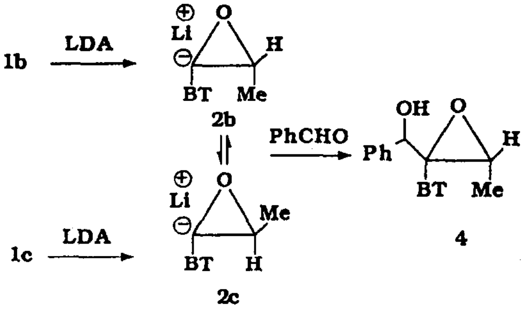
Table. Reaction of oxiranyllithiums **2a-c** with electrophiles in THF at -90°C.

Oxiranyl lithium	Electro- phile	Reaction product (% yield) [a]	anti/syn ratio
2a	Me_3SiCl	**3a** (90)	
"	MeI	**1d** (50)	
"	Cyclopentanone	**3b** (63)	
"	PhCHO	**3c** (83)	75/25
"	$2,6Cl_2C_6H_3CHO$	**3d** (78)	68/32
"	CH_3CHO	**3e** (61)	64/36
"	2-Cyclopentenone	**3g** (37) + **3h** (16)	
2b	PhCHO	**4** (28)	
2c	"	**4** (35)	

a) Yields calculated on isolated products.

It is worth noting that the deprotonation reactions of **1b** or **1c** with **n**-BuLi took place with comparable rates and subsequent reaction of the resulting oxiranyllithiums **2b** and **2c** with benzaldehyde led to the same epoxy alcohol **4**, having the **Z** geometry, as established by NOE difference spectroscopy.[8] As an explanation of this stereoconvergency we may assume that the organolithiums **2b** and **2c** equilibrate and the attack of the benzaldehyde on the oxiranyllithium would take place from the less sterically hindered site of the equilibrating oxiranyllithiums to give **4**.[9]

This finding only apparently contrasts with the recent observation of Molander asserting that the rate of deprotonation of disubstituted cis epoxides is higher than that of the trans isomers for steric hindrance in the base-epoxide complex.[2] In the case of epoxides **1b** and **1c**, it is likely that the highly acidifying effect of the BT group probably makes the relevant deprotonation rates comparable. Moreover, concerning the configurational stability of the oxiranyllithiums **2b** and **2c**, the conjugation with the aza group of the heterocyclic ring might facilitate the interconversion in contrast with the reported configurational stability of many oxiranyllithiums.[9]



In conclusion we wish to point out that the BT group acts as a good stabilizing group for oxiranyllithiums, thus allowing various functionalization of the relevant epoxide. The present paper reveals a new aspect of the reactivity of the alkyl groups in the 2 position of the benzothiazole. Moreover, the benzothiazolyl facilitated lithiation of **1** might represent a useful procedure for the functionalization of epoxides, should the deblocking of the benzothiazole moiety[10] occur under conditions leaving untouched the oxirane ring.

Acknowledgements: We thank Ministero Università e Ricerca Scientifica (MURST) and Italian CNR (Rome) for financial support and Prof. Giovanna Gasparri Fava of the University of Parma, Italy, for the X-Ray analysis.

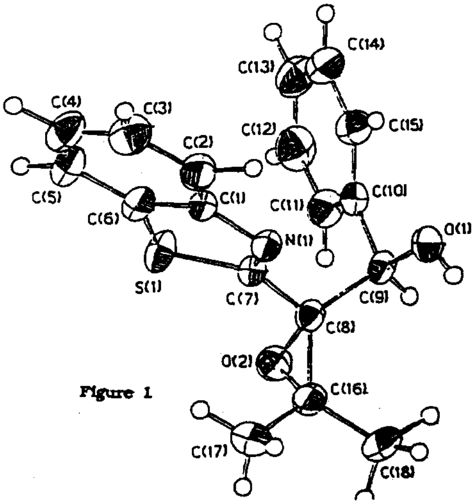
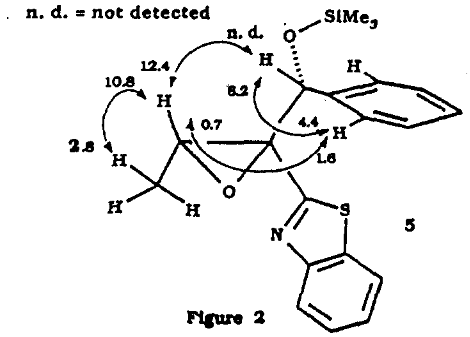


Figure 1

References:

1) A.S. Rao, S.K. Paknikan, J.G. Kirtane, Tetrahedron, 1983, 39, 2323 ; J.G. Smith, Synthesis, 1984, 629 .

2) G.A. Molander and K. Mautner, J.Org.Chem., **1989**, 54, 4042 and Refs. therein.
3) C.A. Cope, P.A. Trumbull and E.R. Trumbull, J.Am.Chem. Soc., **1958**, 80, 2844 J.K.Crandall and L.-H.C. Liu, J.Am.Chem.Soc., **1967**, 89, 4526 ; ibid., **1967**, 89, 4527 ; J.K. Crandall and M. Apparu, Org. React., **1983**, 29, 345 and refs. therein.
4) P.Lohse, H.Loner, P.Acklin, F. Sternfeld, A. Pfaltz, Tetrahedron Lett., **1991**, 32, 615.
5) S. Florio, G. Ingrosso, L. Ronzini and E. Epifani, Tetrahedron, **1991**, 47, 3365
6) S.Florio, L. Troisi, Tetrahedron Lett., in press.
7) General procedure for the reaction of oxiranyllithiums **2** with electrophiles. The reaction of oxiranyllithium **2a** with PhCHO is here described as an example. A solution of **1a** (1.46 mmole) in 5 ml of THF at -90°C under nitrogen atmosphere was added dropwise to a solution of lithium diisopropylamide (LDA) (1.90 mmole) in 10 ml of THF. After 5 min a solution of benzaldehyde (1.90 mmole) in 3 ml of THF was added dropwise. The reaction mixture was kept at -90°C for 30 min and then allowed to warm at room temperature and quenched with a aqueous sat solution of NH_4Cl. Extraction with ether (2 x 25 ml), drying over $MgSO_4$ and evaporation of the solvent under reduced pressure left a residue that was a mixture of 3c(anti) and 3c(syn) that were separated by column chromatographed using ether-petroleum ether mixture of increasing polarity starting from petroleum ether as eluent.
   All new compounds showed consistent NMR, IR data and satisfactory microanalytical data.
8) The methynic ring proton of compound **5**, obtained by silylation of **4** with Me3SiCl, displays a dipolar interaction with the proton geminal to the phenyl ring (the saturation of this latter gives 12.4 % enhancement of the ring proton resonance, although the reverse experiment gives no detectable enhancement). The orientation of the ring proton is confirmed by the detection of small but unquestionable dipolar interactions also with the ortho phenyl protons (1.6 % enhancement of the ortho proton resonance from irradiation of the ring proton, 0.7 % enhancement of the resonance of the latter in the reverse experiment) (Figure 2).



5

Figure 2

9) For the configurational stability of oxiranyllithiums see Ref.2 and J.J.Eisch and J.E.Galle, J. Org. Chem., **1990**, 55, 4835 . Some cis-trans isomerization of lithiated phenylsulfonyl oxiranes has been reported: M. Ashwell, W. Clegg and R.F.W. Jackson, J. Chem. Soc. Perkin Trans 1, **1991**, 897
10) The deblocking reaction of the benzothiazole group has been reported: E. J. Corey and D.L. Boger, Tetrahedron Lett., **1978**, 5

(Received in UK 4 November 1992)