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2-BENZOTHIAZOLYLCHLOROMETHYLLITHIUM: SYNTHESIS OF OXIRANES

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Abstract: Deprotonation of 2-chloromethylbenzothiazole **1** with lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at -78°C gives a red solution of 2-benzothiazolylchloromethyllithium **2**, which couples with carbonyl compounds furnishing oxiranes **3**.

2-Benzothiazolyl substituted oxiranes of the kind **3**, potential precursors of more fuctionalized benzothiazole derivatives as well as of formyl and acyl substituted oxiranes upon deblocking of the thiazole ring,[1] cannot be prepared by direct epoxidation of the relevant vinyl derivatives, due to the competitive and predominant oxidation of the aza-group of the heterocyclic ring.[2] A recent synthesis (the only one reported sofar) goes through a number of steps involving the preparation of 2-allylbenzothiazoles, isomerisation to the corresponding vinyl derivatives, their conversion into the corresponding bromohydrins and cyclisation under basic conditions.[3]

In the present communication we describe a novel, one step synthesis of oxiranes **3**, based on the coupling reaction of 2-benzothiazolylchloromethyllithium **2** with carbonyl compounds.

Lithiation of 2-chloromethylbenzothiazole **1**[4] with LDA in THF at -78°C furnished a dark red solution of the organolithium **2** that could be trapped either by methylation with MeI to give **4a** (82% yield) or by silylation with Me_3SiCl to give **4b** (50% yield)[5] (see Table). The rather easy generation of **2** by lithiation of **1** is to be ascribed to the stabilization provided by both the chlorine and the heterocyclic group to the carbanionic species.[6] The reaction of **2** with acetaldehyde afforded quite good yield of the epoxide **3a** . Organolithium **2** was generated by addition of LDA to **1** in the presence of CH_3CHO (Barbier technique).[7]

Lower yield was obtained when the coupling of **2** with CH3CHO was carried out by the Grignard technique (first generation of **2** with LDA and then addition of the electrophile).

BT–CHRR'

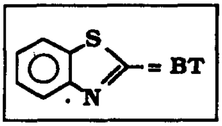
1 : R = Cl; R' = H

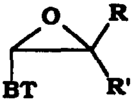
2 : R = Cl; R' = Li

4a : R = Cl; R' = Me

4b : R = Cl; R' = $SiMe_3$

4c : R = OH; R' = H





3a : R = Me ; R' = H

3b : R = Ph ; R' = H

3c : R = $mClC_6H_4$; R' = H

3d : p $CF_3C_6H_4$; R' = H

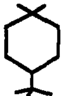
3e : R = $mNO_2C_6H_4$; R' = H

3f : R = R' = C_6H_5

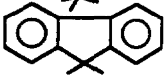
3g : R = R' = Me

3h : R, R' =

3i : R, R' =

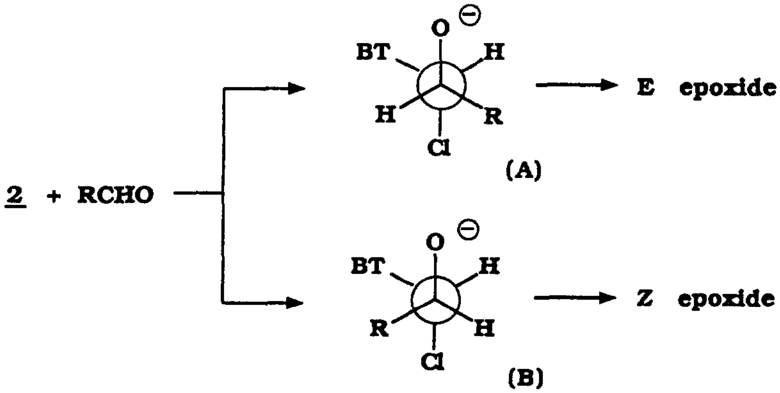


3l : R, R' =



3m : R, R' =

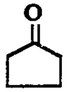
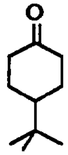
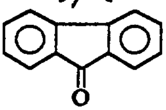
The reaction of **2** with acetaldehyde took place in a stereoselective fashion leading almost exclusively to the epoxide **3a** having **E** configuration.[8] The formation of the intermediate chloroalkoxide offers a plausible interpretation of such a diastereoselectivity. The organolithium **2** may differentiate between the two enantiofaces of the aldehyde in the step leading to the chloroalkoxides (A) and (B). Transition state preceding the formation of (A), the precursor of the **E** epoxide, should be energetically favoured because it experiences a lower steric compression. Equally high yield and **E** diastereoselective was the coupling of **2** with benzaldehyde leading to the epoxide **3b**.[8] The coupling reaction of **2** works well either with aliphatic and aromatic aldehydes



It was observed that **2** couples with ketones leading to the corresponding oxiranes in very good yields. As can be seen from the table the reaction works well with enolizable and not enolizable as well as with acyclic and strained cyclic ketones. A low yield of the relevant epoxide was observed in the reaction of **2** with fluorenone, likely due to steric hindrance at the carbonyl centre.[9] It is worth noting that the coupling of **2** with 4-terbutylcyclohexanone took place with excellent diastereoselectivity producing just one of the two possible diastereoisomers **3i** even though at present we cannot say which is its configuration.[10]

In conclusion we have here reported a novel and high yield route to benzothiazolyl substituted oxiranes which may have a potential for the preparation of functionalized benzothiazoles as well of formyl and acyl substituted epoxides. In view of the easy generation of 2-benzothiazolylchoromethyllithium **2**, work is in progress in this laboratory to further investigate the chemistry of this kind of α-halometalcompound.

$$\mathrm{BTCH_2Cl} \xrightarrow{\textbf{Electrophile (E) / LDA}}$$

E	Reaction product	% yield[a]	E	Reaction product	% yield[a]
CH_3I	**4a**	82	$(C_6H_5)C{=}O$	**3f**	60
Me_3SiCl	**4b**	50	$(CH_3)_2C{=}O$	**3g**	>95
CH_3CHO	**3a**	78		**3h**	75
C_6H_5CHO	**3b**	82		**3i**	80
$mClC_6H_4CHO$	**3c**	65		**3l**	~10
$pCF_3C_6H_4CHO$	**3d**	70			
$mNO_2C_6H_4CHO$	**3e**	68		**3m**	65

a) yields calculated on isolated products.

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References

1) The deblocking of the benzothiazole ring has been described: E.J. Corey and D.L. Boger, **Tetrahedron Lett.**, 5 (1978).
2) S. Takahashi and H. Kano, **Chem. Pharm. Bull.**, **17**, 1598 (1969); H.J. Anderson, D.J. Barnes and Z.M. Khan, **Can. J. Chem.**, **42**, 2375 (1964).
3) S. Florio, G. Ingrosso, L. Ronzini and E. Epifani, **Tetrahedron**, **47**, 3365 (1991).
4) Chloromethylbenzothiazole **1** was prepared from 2-benzothiazolyl carbinol[11] (1 mole) and $SOCl_2$ (3 mole) in CH_2Cl_2 at room temperature till the disappearance of **1**.
5) Chlorosilane **4b** tends to undergo desilylation to give **1**.
6) In the absence of another stabilizing group α-haloorganolithiums are normally generated by lithium-halogen exchange (G. Cainelli, A. Umani Ronchi, F. Bertini, P. Grasselli and G. Zubiani, **Tetrahedron**, 27, 6109 (1971)) or by fluoride ion-catalysis from α-haloorganosilanes (M. Fujita, M. Obayashi and T. Hiyama, **Tetrahedron**, 44, 4135 (1988)).
7) Typical procedure: the reaction of **2** with benzophenone is here described as an example. To a 10 ml THF solution of diisopropylamine (2.4 mmole) was added at O°C 1 ml of 2.4M n-BuLi. The resulting solution was cooled at -78°C and then added dropwise with a THF solution of **1** (O.366 g, 2.0 mmole) and benzophenone (0.440 g, 2.4 mmole) in 10 ml of THF. After 1h at -78°C the reaction mixture was allowed to warm to RT and quenched with an aqueous sat solution of NH_4Cl. Extraction with ether (3x25 ml), drying over Na_2SO_4 and evaporation of the solvent under reduced pressure left a residue that was column chromatographed (E.P./E.E. : 8.5/1.5 as eluent) to give diphenylbenzothiazolyl oxirane **3f** (60% yield).
8) The stereochemistry of **3a** was assigned on the basis of the coupling constants between the two ring hydrogens(see Ref. 3).
9) E.J. Corey, M. Jautelat and W. Oppolzer, **Tetrahedron Lett.** 2325 (1967).
10) The oxiranes prepared by the present procedure and not known in the literature showed consistent IR, ^{1}HNMR and MS data.
11) H. Chikashita, S. Ikegami, T. Okumura and K. Itoh, **Synthesis**, 375 (1986)

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