

REACTION OF 2-LITHIOBENZOTHAZOLE WITH ELECTROPHILES AND
A SYNTHESIS OF α -HYDROXY ALDEHYDES AND KETONES

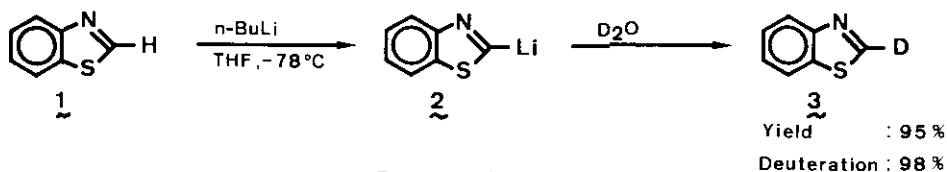
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Abstract — The reaction of 2-lithiobenzothiazole with a variety of electrophiles, except for alkyl halides and styrene oxide, could be effectively accomplished to give the expected products in high yields. The adducts of lithiobenzothiazole to carbonyl compounds could be effectively transformed into α -hydroxy aldehydes and ketones through three steps without masking the α -hydroxy group.

The convergent synthesis of carbonyl compounds by using 2-lithio-1,3-dithiane¹⁻³ and related reagents⁴ as acyl anion equivalent has been the subject of considerable recent interest. These impressive synthetic tools have been widely used at various synthetic stages since it was first reported in 1965 by Corey and Seebach.¹ On the other hand, benzothiazole ring system (hereafter denoted as BT) is also of importance as a masked carbonyl function.⁵ However, despite much work in the BT field, only one example of one-carbon homologation of electrophile by using BT has been reported from the stand point of this concept.⁵ Thus, we thought it important to examine the nucleophilicity of 2-lithio BT to electrophiles on account of the development of this methodology. In this paper, we wish to report the reactions of 2-lithio BT prepared by lithiation of BT with various electrophiles and show the characteristic nucleophilicity of 2-lithio BT in these reactions. Furthermore we wish to exemplify the utility of the products obtained from the reaction of 2-lithio BT with carbonyl compounds with respect to the synthesis of α -hydroxy aldehydes and ketones.

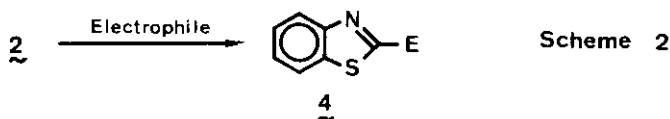
Conversion of BT to 2-Lithio BT. The conversion of BT (1) into 2-lithio BT (2) was most conveniently achieved by adding 1.1 molar amount of *n*-butyllithium to a solution of 1 in THF at -78°C . The progress of the lithiation can be followed by



Scheme 1

deuteration of the reaction solution. When we determined the degree of deuterium incorporation by ^1H -nmr spectroscopy after the reaction solution was deuterated as soon as *n*-butyllithium was added, BT-2-d (**3**) was obtained in 95% yield with 98% deuteration (Scheme 1). This shows that metalation of **1** immediately occurs in quantitative yield. Accordingly, in the following experiments, electrophiles were added to the anion solution immediately after the addition of *n*-butyllithium. The solution of **2** is clear and orange-colored.

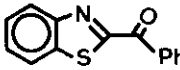
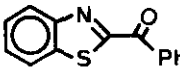

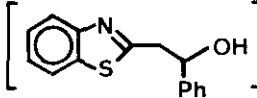
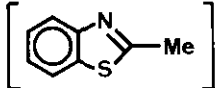
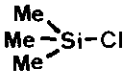
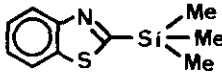
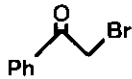
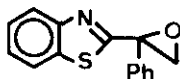
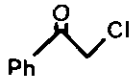
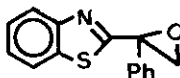
Reaction of 2-Lithio BT with Various Electrophiles. The reactions of **2** with various electrophiles except for carbonyl compounds were first examined under the reaction conditions shown in Table 1 (Scheme 2). Acylation of **2** with ethyl



Scheme 2

benzoate was performed in good yield to give 2-benzoyl BT. Similarly, the reaction of **2** with benzonitrile afforded 2-benzoyl BT after acidic work-up. In contrast to acylation of 2-lithio-1,3-dithianes³ with esters in which a large excess of acylating reagent is required in order to avoid the abstraction of a proton in the primary product by excess lithium reagent or the formation of diadduct, 1.1 equiv of the ester were sufficient to conduct the acylation. The reaction of styrene oxide with **2** did not lead to the formation of β -hydroxy BT derivative and **1** was recovered after quenching by water. Although trimethylsilyl chloride reacted readily with **2** to give 2-trimethylsilyl BT in quantitative yield, attempts to alkylate **2** to the corresponding 2-alkylated BT with alkyl halides were unsuccessful. Thus, in the present conditions, common alkyl halides can not be used successfully in these alkylations. In order to assess the nucleophilic nature of **2** in detail, the reaction of **2** with phenacyl chloride or phenacyl bromide was carried out. Interestingly, the epoxy derivative was selectively obtained in high yield. This result evidently shows that the product is formed by nucleophilic attack of **2** to the carbonyl carbon followed by intramolecular cyclization, and suggests that

Table 1. The reaction of 2-lithio BT with electrophiles.

Electrophile	Conditions	Product (4)	Yield(%) [*]
PhCOOEt	-78°C, 1 hr		7.6
PhCN	1) -78°C, 1 hr 2) H ₃ O ⁺		8.2
	-78°C, 3 hr - r.t.		no reaction
MeI	-78°C, 3 hr - r.t.		no reaction
	-78°C, 2 hr - r.t.		9.6
	-78°C, 1 hr - r.t.		6.7
	-78°C, 1 hr - r.t.		9.2

* Yield of isolated, pure product.

nucleophilicity of **2** toward halogenated carbon is very low. It should be noted that the reactions of **2** with 1,2-oxide or alkyl halides at higher temperature is generally unavailable and unsatisfactory because a solution of **2** is unstable above -40°C.

α -Hydroxyalkylation of 2-Lithio BT with Aldehydes and Ketones. Table 2 lists the results of the reaction of **2** with aldehydes or ketones. The reaction almost proceeded within an hour at -78°C, and the reaction time did not vary with the steric and electronic characters of carbonyl compounds. Under present conditions, readily enolized ketone, such as cyclohexanone, gave the product of carbonyl addition in high yield (run 8). This demonstrates the very effective nucleophilicity of the lithium reagent. Although the reactions of **2** with several carbonyl compounds were previously described,⁶ present method constantly affords higher yields of products. Lithiated BT shows a high preference for the 1,2-addition to α,β -

unsaturated carbonyl compounds (runs 9 - 11).

An Application to the Synthesis of α -Hydroxy Aldehydes and Ketones. α -Hydroxy aldehyde (9) and α -hydroxy ketone (10) were derived from α -hydroxy BT (5a) in good yields as shown in Scheme 3. Thus, methylation of the α -hydroxy BTs (e.g. 5a) was

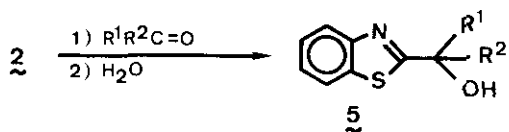
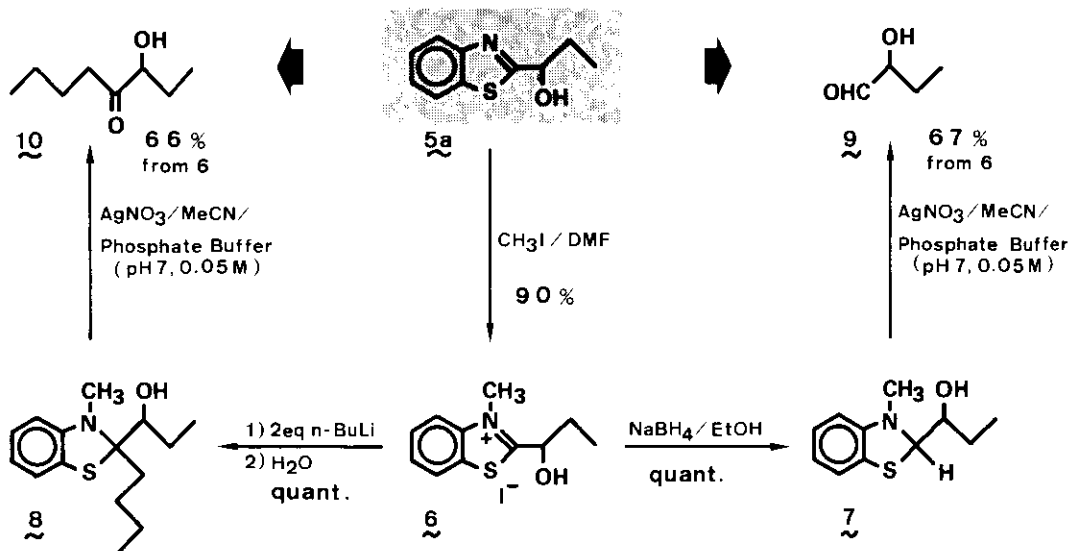


Table 2. The reaction of 2-lithio BT with carbonyl compounds^{a)}

Run	Carbonyl compound	Product (5)	Yield (%) ^{b)}	mp (°C)
1			70	102.0-102.5
2			85	110.0-111.0
3	Ph-CHO		77	124.5-125.0
4			73	155.0-155.5
5			88	80.5-81.0
6			88	Oil
7			88	Oil
8			78	106.5-107.0
9			50	105.0-106.0
10			71	143.7-144.5
11	Ph-C≡C-C(=O)CH ₃		78	134.3-135.0

a) Reaction conditions: benzothiazole; 50 mmol, n-BuLi; 55 mmol, carbonyl compound; 55 mmol, solvent; THF, temp., -78°C, time; 2 hr.

b) Yield of isolated, pure product.



easily accomplished by the treatment with 6.0 equiv of methyl iodide in DMF (0.38 ml/ mmol substrate) at reflux temperature afforded the salts (e.g. 6) in high yields.⁷ The reduction of these salts could be carried out with sodium borohydride in ethanol at room temperature for an hour to give N-methylbenzothiazolines (e.g. 7) in quantitative yields. Alternatively, we found that the salts reacted with 2 equiv of organolithium reagents (e.g. *n*-BuLi, C₇H₁₅C≡CLi) to afford 2,2-disubstituted N-methylbenzothiazolines (e.g. 8) in near quantitative yields. Hydrolysis of crude N-methylbenzothiazolines (e.g. 7, 8) to the respective α-hydroxy aldehyde (e.g. 9) and ketone (e.g. 10) could be accomplished in good yields by the treatment with AgNO₃ in aq. CH₃CN buffered to pH 7 followed by neutralization (1.0 equiv of Et₃N) of the acid (HNO₃) released.⁸

Further studies on the scope and limitations of the present reaction, as well as applicability in organic synthesis, are now in progress.

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5. E. J. Corey and D. L. Boger, Tetrahedron Lett., 1978, 5.
6. H. Gilman and J. A. Beel, J. Am. Chem. Soc., 1949, 71, 2328.
7. Methylation of α -hydroxy BTs derived from ketones was more sluggish than that of α -hydroxy BTs derived from aldehydes and required longer reaction time, but afforded satisfactory yields (>70%) of the salts.
8. This method was previously reported for the hydrolysis of N-methyl-vinyl-benzothiazolines; reference 5.

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