  Bull. Chem. Soc. Jpn., 62, 1215—1225 (1989)

Nonacidic and Highly Chemoselective Protection of the Carbonyl Function. 3-Methylbenzothiazolines as a Base- and Acid-Resistant Protected Form for the Carbonyl Groups

Hidenori CHIKASHITA,* Shun-ichiro KOMAZAWA, Nishiki ISHIMOTO, Koji INOUE, and Kazuyoshi ITOH

Department of Applied Chemistry, Faculty of Engineering, Kansai University, Suita, Osaka 564

(Received November 21, 1988)

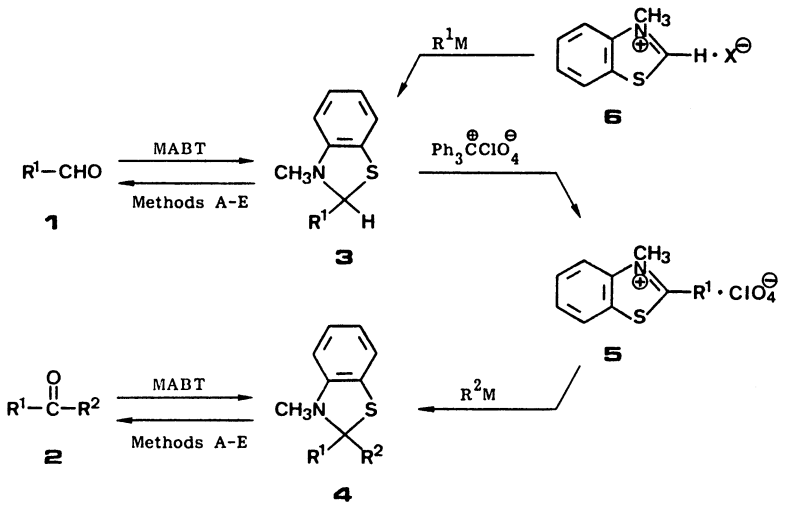
A simple and useful new type of protection method for carbonyl groups by conversion into 3-methylbenzothiazoline derivatives with *o*-(methylamino)benzenethiol was described. With this method, 3-methylbenzothiazolines were conveniently obtained in excellent yields from various aldehydes and ketones. This method allows efficient protection and deprotection under mild and neutral conditions and affords protection of the carbonyl group against both basic and acidic conditions. The difference in reactivity between different carbonyl groups was successfully utilized for the chemoselective benzothiazolination of the formyl group of 4-oxopentanal and also for the chemoselective conversion of 4-androstene-3,17-dione and progesteron into the corresponding benzothiazolines with the nonconjugated keto groups remaining intact. 2-Substituted benzothiazolines derived from aldehydes were efficiently converted into 2,2-disubstituted benzothiazolines via alkylation, with a variety of Grignard or organolithium reagents, of 2-substituted 3-methylbenzothiazolium salts which were readily obtained by the treatment of the former thiazolines with trityl perchlorate in acetonitrile. These salts were also obtained in good yields from aldehydes in one-pot syntheses by the treatment with *o*-(methylamino)benzenethiol in acetonitrile followed by addition of trityl perchlorate. 3-Methylbenzothiazolium iodide was found to be also effective as a formyl cation equivalent and the reactions with Grignard or organolithium reagents produced the corresponding 2-substituted benzothiazolines in good yields. With this reaction, 2-deuterio-3-methylbenzothiazolium iodide was effectively applied as a deuterated formyl cation equivalent for the synthesis of aldehyde-*d*.

The protection of carbonyl groups as acetals is now widely and frequently used as an important synthetic operation during the course of various synthetic projects. Acetalization of carbonyl compounds is generally performed in the presence of various acidic catalysts and the protected form is known to be very stable under various basic conditions while it can be easily deprotected by treating with acid.[1] However, this simplicity is disadvantageous at the same time because acetalized compounds can not be treated with acid except for removing the protection and in addition, acid-sensitive molecules can not be protected and deprotected as acetals. Furthermore, a convenient and at the same time highly chemoselective acetalization method capable of discrimination between aldehydes and ketones has not yet been achieved in spite of its great importance and necessity.[2] On the other hand, thioacetalization is an important and widely used protecting method for carbonyl compounds as well as acetalization. However, this method is also not exempted from some of these disadvantages.

In this paper, we report a new type of convenient and highly chemoselective protection of carbonyl compounds by conversion into 3-methylbenzothiazoline derivatives with *o*-(methylamino)benzenethiol (MABT). This method allows efficient protection and deprotection under mild and neutral conditions and affords protection of carbonyl groups against both basic and acidic conditions. We will also show that the benzothiazoline ring system is very useful as a functional protective group via 3-methylbenzothiazolium salts (**5** and **6**) as an acyl and a formyl cation equivalent (Scheme 1).

Benzothiazolination of Aldehydes and Ketones with MABT. In order to establish optimum conditions, the rates of benzothiazolination for pentanal (**1a**) and 2-pentanone (**2a**) with one equiv of MABT in various solvents at reflux temperatures were followed by GLC. The results are presented in Figs. 1 and 2. Regarding the benzothiazolination of aldehyde **1a**, the reaction proceeded using a protic or an aprotic solvent in excellent yields (>88%) during the 6 h reaction time and the rates did not vary significantly based on type of solvent (Fig. 1). However, ethanol was apparently the most effective and the reaction proceeded almost quantitatively during the 6 h reaction time even in 98% ethanol. On the other hand, the reaction of ketone **2a** with MABT occurred more slowly as compared to **1a** and did not proceed in hexane at all. Although the reaction rates varied considerably based on type of solvent, the rate in alcohols or acetonitrile was sufficiently rapid to be synthetically useful for the protection of ketones (Fig. 2). The different reactivity of **1a** and **2a** is advantageous from a synthetic viewpoint since it enables the selective protection of aldehydes in the presence of ketones. It is noteworthy and very attractive that these reactions were performed under neutral conditions without any additives by a very simple operation which does not require even the removal of the water formed during the reaction.

By this simple method, benzothiazolinations of several aldehydes were successfully performed with the



Scheme 1.

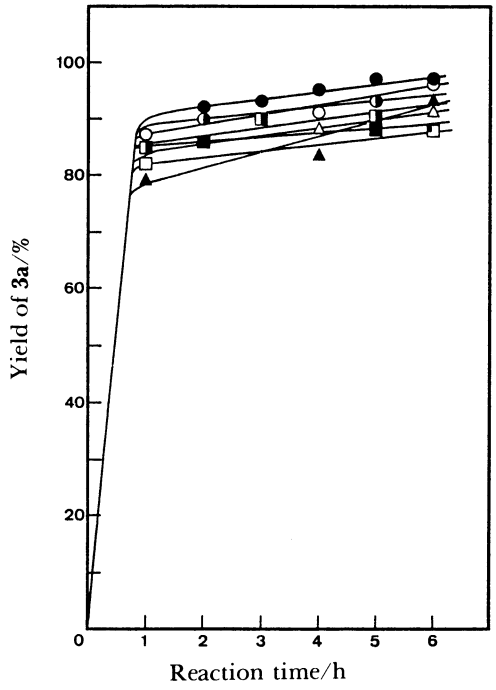


Fig. 1. Benzothiazolination of pentanal (**1a**) with one equiv of MABT in various solvents at reflux temperatures: ethanol (●), 98% ethanol (○), methanol (◑), acetonitrile (▲), THF (△), dichloromethane (■), benzene (□), and hexane (◧).

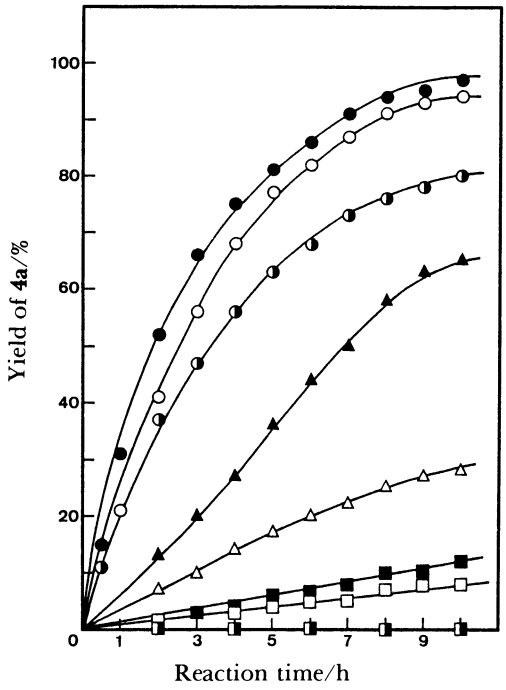
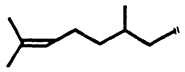


Fig. 2. Benzothiazolination of 2-pentanone (**2a**) with one equiv of MABT in various solvents at reflux temperatures. Symbols are identical with those used in Fig. 1.

results summarized in Table 1. As is seen in Table 1, aliphatic as well as aromatic aldehydes **1a**—**k** were all cleanly converted to the corresponding 2-substituted benzothiazolines **3a**—**k** with MABT in ethanol. Unexpectedly, the benzothiazolination of conjugated enal (**1l**) proceeded very slowly under the present conditions to afford **3l** in low yield. Benzothiazolination with MABT in ethanol was also examined with several ketones and the results are listed in Table 2. The linear ketones **2a**—**e** except for highly hindered ketone, 2,4-dimethyl-3-pentanone (**2f**) which almost did not react, were all cleanly converted to the corresponding 2,2-disubstituted benzothiazolines **4a**—**e** in almost quantitative yields. In the case of linear conjugated enones **2i** and **2j**, the reaction proceeded very slowly and much of the substrate was recovered unchanged. It is noteworthy that the benzothiazolination of the cyclic ketone **2g** and cyclic enone **2h** proceeded much more rapidly than the linear ketones and enones to afford **4g** and **4h** in quantitative and good yields, respectively. Thus, the order of relative reactivity of ketones in the present benzothiazolination was as

Table 1. Preparation and Hydrolysis of 2-Substituted Benzothiazolines **3**

R^1	Aldehyde	Benzothiazoline	Benzothiazolination[a]		Hydrolysis[b]
			Time/h	Yield/%[c]	Yield/%[d]
n-C_4H_9-	**1a**	**3a**	6	87	—
n-C_9H_{19}-	**1b**	**3b**	24	82	86
n-$C_4H_9(C_2H_5)CH$-	**1c**	**3c**	24	84	83
	**1d**	**3d**	24	85	93
i-C_3H_7-	**1e**	**3e**	6	91	—
t-C_4H_9-	**1f**	**3f**	24	89	—
C_6H_5-	**1g**	**3g**	6	80	95
p-ClC_6H_4-	**1h**	**3h**	6	86	—
p-$CH_3OC_6H_4$-	**1i**	**3i**	6	82	—
	**1j**	**3j**	6	85	96
	**1k**	**3k**	6	90	94
(Z)-C_6H_5CH=CH-	**1l**	**3l**	24	28	84

a) Aldehyde (5 mmol) was reacted with MABT (5 mmol) in ethanol (5 ml) at reflux temperature. b) Hydrolysis was carried out under the conditions of Method A (see Table 3). c) Yield of pure product after short column chromatography or recrystallization. d) Yield of crude, nearly pure product.

Table 2. Preparation and Hydrolysis of 2,2-Disubstituted Benzothiazolines **4**

R^1	R^2	Ketone	Benzothiazoline	Benzothiazolination[a]		Hydrolysis[b]
				Time/h	Yield/%[c]	Yield/%[d]
n-C_3H_7-	CH_3-	**2a**	**4a**	10	88	—
n-C_3H_7-	n-C_3H_7-	**2b**	**4b**	10	90	—
n-C_5H_{11}-	n-C_5H_{11}-	**2c**	**4c**	24	90	94
i-C_3H_7-	CH_3-	**2d**	**4d**	24	91	—
C_6H_5-	CH_3-	**2e**	**4e**	10	89	90
i-C_3H_7-	i-C_3H_7-	**2f**	**4f**	24	Trace	—
-$(CH_2)_5$-		**2g**	**4g**	4	97	92
-CH=$CH(CH_2)_3$-		**2h**	**4h**	24	69	92
(E)-C_6H_5CH=CH-	CH_3-	**2i**	**4i**	24	32	90
(E)-C_6H_5CH=CH-	C_6H_5-	**2j**	**4j**	24	21	98

a) Ketone (5 mmol) was reacted with MABT (5 mmol) in ethanol (5 ml) at reflux temperature. b) Hydrolysis was carried out under the conditions of Method A (see Table 3). c) Yield of pure product after short column chromatography or recrystallization. d) Yield of crude, nearly pure product.

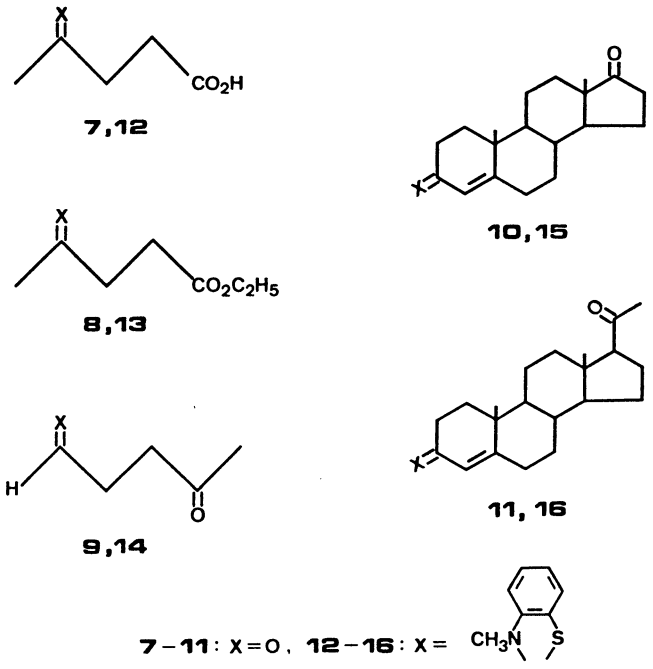
follows: cyclohexanone > linear ketones > 1-cyclohexen-1-one > linear conjugated enones > 2,4-dimethyl-3-pentanone.

Selective Benzothiazolination of Carbonyl Groups in the Presence of a Different Carbonyl Group. In order to examine the selectivity of the present benzothiazolination with MABT, experiments with compounds having two different carbonyl groups were performed (Scheme 2). As seen in the successful conversion of the keto carboxylic acid **7** and the keto ester **8** into the corresponding benzothiazolines **12** and **13** (94 and 92% yields, respectively) with one equiv of MABT in ethanol at reflux temperature, the benzothiazolination of keto groups can be easily performed in the presence of carboxylic acid or similar ester functional group. The benzothiazolination by the same method also exhibited splendid selectivity towards the formyl group. For example, the reaction of keto aldehyde **9** gave **14** as the sole product in 99% yield. The striking chemoselectivity of the present method was also emphasized by the fact that perfect selectivity could be realized in the benzothiazolination of steroid ketones **10** and **11** to **15** and **16** in dichloromethane and ethanol, respectively, with one equiv of MABT at reflux temperatures. After completion of the reactions, the products **15** and **16** were obtained in 93 and 97% yields, respectively and neither starting materials nor any by-products derived from the benzothiazolination at the nonconjugated keto carbonyl group was observed. These excellent chemoselectivities are in sharp contrast to acetalization or thioacetalization of the same steroid ketones.[3]

Hydrolysis and Stabilities of Benzothiazolines. Hydrolysis of benzothiazolines to the parent carbonyl

compounds was examined using two test substances **3g** and **4e**. As shown in Table 3, the hydrolysis could be effectively accomplished under neutral conditions in four ways (Methods A—D) using $AgNO_3$, $HgCl_2$, NBS, and Chloramine T to afford benzaldehyde (**1g**) and acetophenone (**2e**) in excellent yields, although the hydrolysis of **4e** by Method D gave exceptionally low yield of **2e**. Using another method, methylation with $MeOSO_2F$ followed by hydrolysis under mildly basic conditions was also effective to afford the products **1g** and **2e** in excellent yields. Notable in the case of Method A is the fact that such mild conditions did not affect the epimerizable center[4] or the α-hydroxyl group.[5] In addition, the mild nature of Method A is also illustrated in the conversion of 2-(β-hydroxyalkyl)-benzothiazolines **17** and **18** to the corresponding β-hydroxy ketones **19** and **20** (88 and 94% yields, respectively) without any evidence of dehydration (Scheme 3). Further results for the deprotection of benzothiazolines using Method A are given in Tables 1 and 2. All the tested benzothiazolines derived from aldehydes and ketones were cleanly cleaved with no difficulties and produced the corresponding carbonyl compounds in nearly quantitative yields.

Stabilities of the benzothiazolines were checked using **3g** and **4b** as samples. As shown in Table 4, both of these compounds survived the severe conditions

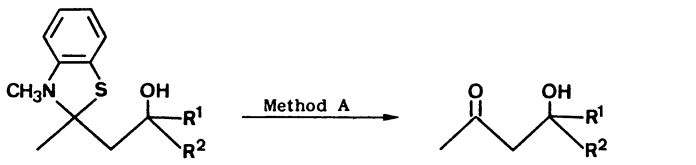


Scheme 2.

Table 4. Stabilities of Benzothiazolines

Reaction conditions	Recovery/%[a]	
	3g	**4b**
$LiAlH_4$/THF/r.t./24 h	94	97
$NaBH_4$/CH_3OH/reflux/24 h	98	94
20% H_2SO_4/70 °C/7 h	99	95
1M KOH/CH_3OH/reflux/7 h	97	93
Al_2O_3/CH_3OH/reflux/24 h	93	97
CF_3COOH/r.t./24 h	95	98
H_2(1 atom)/5% Pd-C/EtOH/r.t./18 h	94	94

a) Yields of the isolated benzothiazolines.



17: $R^1=H, R^2=n\text{-}C_9H_{19}$ **19**: $R^1=H, R^2=n\text{-}C_9H_{19}$

18: $R^1=R^2=CH_3$ **20**: $R^1=R^2=CH_3$

Scheme 3.

Table 3. Methods for Hydrolysis of Benzothiazolines into Aldehydes or Ketones

Method[a]	Reagent	Solvent	Isolated yield/%	
			1g	**2e**
A	$AgNO_3$	aq. CH_3CN	95	90
B	$HgCl_2$	aq. CH_3CN	93	94
C	NBS	H_2O	91	86
D	Chloramine T	C_2H_5OH	85	21
E	CH_3OSO_2F/K_2CO_3	CH_2Cl_2/aq. THF	92	96

a) Method A: benzothiazoline (4 mmol), $AgNO_3$ (12 mmol), CH_3CN-phosphate buffer (pH 7, 0.05 M)-H_2O (15 : 3 : 5 v/v), r.t. for 40 min (for the aldehyde) or r.t. to 40 °C for 100 min (for the ketone), $(C_2H_5)_3N$ (4 mmol). Method B: benzothiazoline (4 mmol), $HgCl_2$ (6 mmol), CH_3CN-H_2O (4 : 1 v/v), reflux temp, 4 h. Method C: benzothiazoline (4 mmol), NBS (8 mmol), H_2O, r.t., 10 min. Method D: benzothiazoline (4 mmol), Chloramine T (4.8 mmol), C_2H_5OH, r.t., 1 h (for the aldehyde) or 24 h (for the ketone). Method E: benzothiazoline (4 mmol), CH_3OSO_2F (4.8 mmol), CH_2Cl_2, r.t., 18 h (for the aldehyde) or 24 h (for the ketones), and then 5% aq. K_2CO_3-THF (4 : 5 v/v), r.t., 4 h.

commonly required for removal of other protecting groups. The resistability to both basic and acidic conditions is especially attractive and increases the importance of the present protection method.

Conversion of 2-Substituted Benzothiazolines 3 into 2,2-Disubstituted One 4 via Benzothiazolium Salts 5 as Acyl Cation Equivalents. During the course of a study about the reactivity of 2-substituted benzothiazolines **3**, we have found that 3-methylbenzothiazolium perchlorates **5** are readily prepared in excellent yields by the reaction of **3** with trityl perchlorate in acetonitrile with the results summarized in Table 5. As shown in Table 5, these easily handled and stable carbocations were also conveniently obtained in good yields from aldehydes by the one-pot reaction with MABT in acetonitrile followed by the addition of trityl perchlorate. In order to demonstrate the possibility of using these salts as an acyl cation equivalent, we have studied the reaction of **5** with a variety of Grignard or organolithium reagents. The results are summarized in Table 6. The conversion of **5** into 2,2-disubstituted benzothiazolines **4** was most conveniently achieved by the addition of 1.2 equiv of Grignard or organolithium reagent to the suspension of **5** in THF or ether at −78 °C. These reactions generally proceeded quite cleanly and nearly pure products were obtained in excellent yields after a simple workup procedure. Thus, by these methods not only alkyl including tertiary but also aryl, allyl, and alkynyl groups were substituted for the hydrogen at the C-2 position of **3**. The ready availability of benzothiazolium salts **5** from aldehydes and facile convertibility of them into 2,2-

Table 5. Conversion of 2-Substituted Benzothiazolines **3** into Benzothiazolium Salts **5**

Substrate	Benzothiazolium salt	Method[a]	Yield/%[b]
3a	**5a** (R^1=C_4H_9)	A	91
3a	**5a**	B	83
3c	**5b** (R^1=$C_4H_9(C_2H_5)CH$)	A	96
3c	**5b**	B	76
3e	**5c** (R^1=*i*-C_3H_7)	A	94
3e	**5c**	B	79
3g	**5d** (R^1=C_6H_5)	A	95
3g	**5d**	B	72
3h	**5e** (R^1=*p*-ClC_6H_4)	A	96
3h	**5e**	B	71
3i	**5f** (R^1=*p*-$CH_3OC_6H_4$)	A	98
3i	**5f**	B	65
3k	**5g** (R^1= )	A	93
3k	**5g**	B	70

a) Method A: Benzothiazoline (5 mmol) was reacted with trityl perchlorate (5 mmol) in acetonitrile at room temperature. Method B (one-pot reaction): Aldehyde (5 mmol) was reacted with MATP (5 mmol) in refluxing acetonitrile followed by the addition of trityl perchlorate (10 mmol). b)Yield of crude, nearly pure product (in Method A). Yield of pure product after recrystallization (in Method B).

Table 6. Alkylation of 2-Substituted Benzothiazolium Salts **5** into 2,2-Disubstituted Benzothiazolines **4**[a]

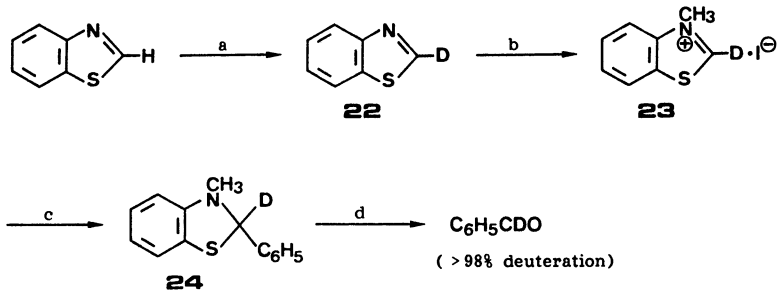
Substrate	R^2M	Product	Solvent	Yield/%[b]
5a	*n*-C_4H_9Li	**4k**	THF	93
5a	*n*-$C_7H_{15}C{\equiv}CLi$	**4l**	THF	92
5a	$C_6H_5C{\equiv}CLi$	**4m**	THF	95
5a	*n*-C_4H_9MgBr	**4k**	THF	92
5a	*t*-C_4H_9MgCl	**4n**	THF	59
5a	C_6H_5MgBr	**4o**	Ether	42[c]
5b	*n*-C_4H_9MgBr	**4p**	THF	87[d]
5c	*n*-C_4H_9MgBr	**4q**	THF	77[d]
5d	*n*-C_4H_9MgBr	**4o**	THF	93[c]
5d	C_6H_5MgBr	**4r**	THF	75[c]
5d	$C_6H_5CH_2MgCl$	**4s**	Ether	88[c]
5f	*n*-C_4H_9Li	**4t**	THF	90
5g	*n*-C_4H_9MgBr	**4u**	THF	99[d]

a) Benzothiazolium salt (4 mmol) was reacted with alkylating reagent (4.8 mmol) at −78 °C (30 min) to room temperature (1 h). b) Yield of crude, nearly pure product unless otherwise noted. c) Yield of pure product after recrystallization. d) Yield of pure product after short column chromatography.

Table 7. Alkylation of Benzothiazolium Salts **6** into 2-Substituted Benzothiazolines **3**[a]

Salt	X	R^2M	Solvent	Product	Yield/%[b,c]
6a	I	*n*-C_4H_9MgBr	THF	**3a**	61[d](70)
6b	SO_3F	*n*-C_4H_9Li	THF	**3a**	(62)[e]
6c	SO_4CH_3	*n*-C_4H_9MgBr	THF	**3a**	(40)
6d	BF_4	*n*-C_4H_9MgBr	THF	**3a**	(32)
6a	I	$(n\text{-}C_4H_9)_2CuMgBr$	THF	**3a**	(64)
6a	I	$CH_2{=}CHCH_2MgBr$	Ether	**3m**	92
6a	I	$CH_3CH{=}CHCH_2MgCl$	THF	**3n**	98[f]
6a	I	$C_6H_5C{\equiv}CLi$	THF	**3o**	90
6a	I	C_6H_5MgBr	THF	**3g**	98
6a	I	*p*-$CH_3OC_6H_4MgBr$	THF	**3i**	95

a) Benzothiazolium salt **6** (4 mmol) was reacted with alkylating reagent (4.8 mmol) at −78 °C (30 min) to room temperature (1 h). b) Yield of isolated, nearly pure product. c) Values in parentheses indicate yields determined by GLC. d) Yield of pure product after short column chromatography. e) Benzothiazolium salt **6** was reacted with the alkylating reagent (4.8 mmol) at −78 °C (30 min) to room temperature (24 h). f) 2-(2-Butenyl)-3-methylbenzothiazoline was selectively obtained.

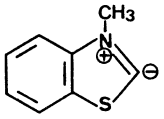


(a) n-BuLi, THF, -78°C, (2) D_2O; (b) CH_3I, DMF, reflux;
(c) C_6H_5MgBr, THF, -78°C-r.t.; (d) Method A (see Table 3).

Scheme 4.

disubstituted benzothiazolines **4** illustrate the synthetic usefulness of the benzothiazoline ring system as a functional protected form for carbonyl groups.

Preparation of 2-Substituted Benzothiazolines 3 by the Reaction of Grignard or Organolithium Reagents with 3-Methylbenzothiazolium Salt 6. 1,3-Dithienium tetrafluoroborate,[6] 2-chloro-1,3-dithiane,[7] and heteroaromatic cations such as 1,3-benzodithiolylium salts[8] are well-known as promising candidates for heterocyclic formyl cation equivalents. However, the reaction of former two compounds with either Grignard or organolithium reagents does not produce or produces with difficulty the corresponding 1,3-dithianes.[7,9] As another synthetic advantage of the benzothiazoline ring system, we have found that Grignard and organolithium reagents react with 3-methylbenzothiazolium salts **6** to give the expected adducts **3** in good yields (Table 7). The reactions were conveniently achieved by a procedure similar to the alkylation of the salts **5**. When **6** was reacted with butylmagnesium bromide or butyllithium, 2-butyl-3-methylbenzothiazoline (**3a**) was most effectively obtained in 70% yield in the case of the reaction using the iodide **6a**. Butylmagnesium cupurate was also used to alkylate **6a** but the yield of **3a** was not improved. The uppermost limit of yields in these reactions is probably due to formation of the ylide **21**



21

derived from proton abstraction from the salt **6** by organometallic reagents. On the other hand, the reaction of **6a** with aryl, allyl, or alkynyl Grignard reagent went to completion yielding the corresponding 2-substituted benzothiazolines in near quantitative yields. Thus, it appears that the reaction of 3-methylbenzothiazolium iodide (**6a**) as a formyl cation equivalent with Grignard or organolithium reagents is a useful way to produce 2-substituted benzothiazolines **3**.

With the aim of evaluating the synthetic potential of **6a**, we present a useful method for the preparation of aldehydes-*d* according to Scheme 4. 2-Deuterated 3-methylbenzothiazolium iodide (**23**) was conveniently prepared in high yield by methylation of benzothiazole-2-*d* (**22**) with iodomethane, which was readily prepared by the lithiation of commercially available benzothiazole with butyllithium followed by quenching with D_2O.[5] The reaction of **23** with phenylmagnesium bromide and subsequent hydrolysis by method A gave benzaldehyde-*d* in excellent yield with almost complete deuterium incorporation. The easy accessibility of **22**, the high yields of the products and the excellent deuterium incorporation offers promise for a new method of synthesizing aldehydes-*d* from Grignard reagents via carbon-carbon bond formation with the deuterated formyl cation equivalent **23**. The deuterated heteroaromatic cation, 2-deuterio-1,3-benzodithiolylium salt, has already been reported as a deuterated formyl cation equivalent for the synthesis of aldehydes-*d* by Degani et al.[10] However, compared with their original method or the improved one,[11] the present method is advantageous because of its high simplicity.

Conclusion

Benzothiazolination with MABT is a very effective, convenient, and mild (no acidic catalyst is required) method for the protection of aldehydes and ketones. The mildness of benzothiazolination and effective convertibility of benzothiazolines into parent carbonyl compounds under neutral and very mild conditions are suitable for the synthetic operation of acid-sensitive multifunctional molecules. High chemoselectivity of benzothiazolination makes the present method more attractive and should be useful for selective protection of carbonyl groups in the presence of a

different carbonyl group. In addition, the resistability of benzothiazolines to both basic and acidic conditions allows one to use the protected form under these conditions. Furthermore, the functionality of the benzothiazoline ring system via benzothiazolium salts as an acyl or formyl cation equivalent increases the value of benzothiazolines in use as a protected form for carbonyl compounds.

Experimental

Melting points were recorded on a Yanagimoto micro melting-point apparatus and are uncorrected. ^{1}H NMR spectra were measured with a JEOL PMX-60 spectrometer at 60 MHz using tetramethylsilane as an internal reference. IR spectra were recorded on a JASCO A-202 spectrophotometer. Mass spectra were obtained on a JMS-QH100 GC-Mass spectrometer. The yields by quantitative GLC were measured on a Shimadzu Gas Chromatograph GC-6AM equipped with a hydrogen flame ionization detector using glass columns (1.5 m) packed with 2% Silicone OV-7 on Uniport HP (60—80 mesh), by the internal standard method using dodecane as an internal standard. Silica gel (Wakogel C-300) was used for short column chromatography.

Materials. Solvents were purified and dried according to standard procedures. MABT was prepared by the reductive ring opening reaction of commercially available benzothiazole with $LiAlH_4$ according to a slightly modified method of Huning et al.[12] Phosphate buffer (0.05 M, pH 7; 1 M=1 mol dm^{-3}) was prepared by dilution of the 0.1 M solution (0.4 M Na_2HPO_4+0.4 M KH_2PO_4) which was commercially available. Trityl perchlorate was prepared by the method of Dauben et al.[13] Carbonyl compounds and the other reagents were obtained as high-grade commercial products.

Benzothiazolination of Aldehydes and Ketones; General Procedure. MABT (0.70 g, 5 mmol) was added to a solution of aldehyde or ketone (5 mmol) in ethanol (5 ml) and the mixture was refluxed for an appropriate reaction time (monitored with TLC; see Tables 1 and 2). The solvent was removed under reduced pressure to give crude product. Purification of the crude oily products (**3a—f, 3l, 4a—d, 4g—j**) and crystalline products (**3g—k, 4e**) was carried out by short column chromatography or recrystallization from ethanol, respectively, to afford pure samples. Product yields are summarized in Tables 1 and 2.

3a: colorless oil; IR (neat) 2940, 1660, 1580, 1670, 1380, 1280, 1120, 1060, and 740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.88 (t, 3H), 1.08—2.08 (m, 6H), 2.67 (s, 3H), 4.78 (dd, 1H), and 6.00—7.00 (m, 4H). Calcd for $C_{12}H_{17}NS$: C, 69.51; H, 8.26; N, 6.76%. Found: C, 69.40; H, 8.55; N, 6.28%.

3b: pale yellow oil; IR (neat) 2900, 2850, 1660, 1580, 1480, 1380, 1300, 1110, 1020, and 740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.87 (t, 3H), 1.03—2.07 (br, 16H), 2.70 (s, 3H), 4.80 (t, 1H), and 6.00—6.90 (m, 4H). Calcd for $C_{17}H_{27}NS$: C, 73.59; H, 9.81; N, 5.05%. Found: C, 73.74; H, 9.92; N, 5.35%.

3c: pale yellow oil; IR (neat) 2940, 1660, 1580, 1480, 1380, 1300, 1110, 1020, 730, and 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ= 0.50—2.17 (m, 15H), 2.70 (s, 3H), 5.12 (d, 1H), and 6.03—7.27 (m, 4H). Calcd for $C_{15}H_{23}NS$: C, 72.23; H, 9.29; N, 5.62%. Found: C, 72.90; H, 8.91; N, 5.81%.

3d: colorless oil; IR (neat) 2900, 1660, 1580, 1480, 1380, 1300, 1110, 1010, and 740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.67—2.17 (m, 16H), 2.67 (s, 3H), 4.87 (m, 2H), and 6.00—6.90 (m, 4H). Calcd for $C_{17}H_{25}NS$: C, 74.13; H, 9.15; N, 5.08%. Found: C, 73.94; H, 9.22; N, 5.13%.

3e: pale yellow oil; IR (neat) 2950, 1660, 1580, 1480, 1380, 1340, 1300, 1220, 1110, 1020, 1000, and 730 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.00 (d, 6H), 2.00 (m, 1H), 2.68 (s, 3H), 5.10 (d, 1H), and 5.84—6.84 (m, 4H). Calcd for $C_{11}H_{15}NS$: C, 68.35; H, 7.82; N, 7.25%. Found: C, 68.33; H, 7.74; N, 7.07%.

3f: colorless oil; IR (neat) 2950, 1570, 1470, 1380, 1350, 1290, 1200, 1120, 1100, 1020, 980, 880, and 740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.90 (s, 9H), 2.90 (s, 3H), 4.42 (s, 1H), and 6.17—6.90 (m, 4H). Calcd for $C_{12}H_{17}NS$: C, 69.51; H, 8.26; N, 6.76%. Found: C, 69.33; H, 8.32; N, 6.58%.

3g: colorless needles; mp 113 °C; IR (KBr) 1580, 1480, 1450, 1340, 1300, 1190, 1110, 1020, 740, and 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=2.70 (s, 3H), 5.80 (s, 1H), and 6.10—7.50 (m, 4H). Calcd for $C_{14}H_{13}NS$: C, 73.97; H, 5.76; N, 6.16%. Found: C, 73.66; H, 5.73; N, 5.90%.

3h: colorless needles; mp 78—78.5 °C; IR (KBr) 1570, 1460, 1400, 1320, 1300, 1260, 1180, 1100, 1080, 1010, 860, 830, 780, and 740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=2.47 (s, 3H), 5.75 (s, 1H), and 6.07—7.40 (m, 8H). Calcd for $C_{14}H_{12}NSCl$: C, 64.24; H, 4.62; N, 5.35%. Found: C, 64.11; H, 4.53; N, 5.22%.

3i: colorless needles; mp 106—106.5 °C; IR (KBr) 1600, 1570, 1510, 1460, 1330, 1280, 1250, 1160, 1100, 1030, 860, 830, 790, and 750 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=2.52 (s, 3H), 3.70 (s, 3H), 5.80 (s, 1H), and 6.33—7.50 (m, 8H). Calcd for $C_{15}H_{15}NOS$: C, 70.01; H, 5.87; N, 5.44%. Found: C, 69.94; H, 5.92; N, 5.29%.

3j: colorless needles; mp 43—43.5 °C; IR (KBr) 2900, 2850, 1580, 1480, 1370, 1300, 1110, 1020, 880, 740, and 710 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.85—2.33 (m, 11H), 3.17 (s, 3H), 4.45 (d, 1H), and 6.84—7.50 (m, 4H). Calcd for $C_{14}H_{19}NS$: C, 72.05; H, 8.21; N, 6.00%. Found: C, 71.48; H, 8.09; N, 5.82%.

3k: colorless needles; mp 89—89.5 °C; IR (KBr) 2900, 1580, 1490, 1430, 1380, 1310, 1220, 1120, 1020, 740, and 670 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.17—2.50 (m, 7H), 2.77 (s, 3H), 5.02 (d, 1H), 5.53 (m, 2H), and 6.00—7.00 (m, 4H). Calcd for $C_{14}H_{17}NS$: C, 72.68; H, 7.41; N, 6.05%. Found: C, 72.36; H, 7.38; N, 5.85%.

3l: colorless oil; IR (neat) 1640, 1570, 1470, 1420, 1340, 1300, 1120, 1040, 1020, 960, 740, and 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=2.67 (s, 3H), 5.43 (dd, 1H), and 6.00—7.33 (m, 11H). This compound is slightly unstable in air.

4a: colorless oil; IR (neat) 2950, 1580, 1480, 1360, 1300, 1120, 1050, 1020, 740, and 720 cm^{-1}; ^{1}H NMR (CCl_4) δ=0.92 (t, 3H), 1.13—2.07 (m, 4H), 1.52 (s, 3H), 2.60 (s, 3H), and 5.87—6.90 (m, 4H). Calcd for $C_{12}H_{17}NS$: C, 69.51; H, 8.26; N, 6.76%. Found: C, 69.41; H, 8.18; N, 6.63%.

4b: colorless oil; IR (neat) 2950, 1580, 1480, 1360, 1300, 1210, 1120, 1050, 1020, and 740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.67—2.00 (m, 14H), 2.60 (s, 3H), and 5.73—6.83 (m, 4H). Calcd for $C_{14}H_{21}NS$: C, 71.44; H, 8.99; N, 5.95%. Found: C, 71.26; H, 8.89; N, 5.91%.

4c: colorless oil; IR (neat) 2900, 1580, 1480, 1360, 1300, 1220, 1120, 1050, 1020, 900, and 730 cm^{-1}; ^{1}H NMR (CCl_4) δ=0.50—2.00 (m, 22H), 2.53 (s, 3H), and 5.73—6.77 (m, 4H). Calcd for $C_{18}H_{29}NS$: C, 74.17; H, 10.03; N, 4.81%. Found: C, 73.99; H, 10.10; N, 4.81%.

4d: pale yellow oil; IR (neat) 1950, 1580, 1480, 1370, 1300, 1220, 1120, 1020, and 740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.94 (d, 6H), 1.55 (s, 3H), 2.03 (m, 1H), 2.58 (s, 3H), and 5.83—6.83

(m, 4H). Calcd for $C_{12}H_{17}NS$: C, 69.51; H, 8.26; N, 6.76%. Found: C, 69.14; H, 8.11; N, 6.66%.

4e: colorless needles; mp 62—63 °C; IR (KBr) 2900, 1580, 1470, 1440, 1370, 1300, 1110, 1040, 1020, 900, 740, and 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.97 (s, 3H), 2.55 (s, 3H), and 6.10—7.67 (m, 9H). Calcd for $C_{15}H_{15}NS$: C, 74.65; H, 6.26; N, 5.80%. Found: C, 74.38; H, 6.29; N, 5.61%.

4g: pale yellow needles; mp 34—34.5 °C; IR (neat) 2900, 1680, 1470, 1360, 1300, 1200, 1100, 1040, 1020, and 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.00—2.23 (m, 10H), 2.67 (s, 3H), and 6.00—7.00 (m, 4H). Calcd for $C_{13}H_{17}NS$: C, 71.18; H, 7.81; N, 6.39%. Found: C, 71.26; H, 7.88; N, 6.27%.

4h: colorless oil; IR (neat) 2900, 1580, 1500, 1480, 1420, 1300, 1210, 1160, 1120, 1030, 960, 740, and 680 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.00—2.13 (m, 6H), 2.60 and 2.73 (each s, 3H), and 6.00—7.33 (m, 6H). Calcd for $C_{13}H_{15}NS$: C, 71.85; H, 6.96; N, 6.44%. Found: C, 71.48; H, 6.88; N, 6.80%.

4i: colorless oil; IR (neat) 2950, 1580, 1470, 1420, 1350, 1300, 1120, 1050, 1020, 960, 740, and 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.73 (s, 3H), 2.58 (s, 3H), and 6.00—7.37 (m, 11H). This compound is slightly unstable in air.

4j: colorless oil; IR (neat) 1580, 1470, 1420, 1360, 1300, 1220, 1120, 1050, 1020, 990, 740, and 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.67 (s, 3H) and 6.13—7.87 (m, 16H). Calcd for $C_{22}H_{19}NS$: C, 80.20; H, 5.81; N, 4.25%. Found: C, 80.36; H, 5.72; N, 4.14%.

Benzothiazolination of Keto Carboxylic Acid 7, Keto Ester 8, and Keto Aldehyde 9. Benzothiazolination of these compounds **7—9** was carried out on a 5 mmol scale for 24 h according to standard procedure. Purification of the crude products which did not contain any by-product or regioisomer (monitored by TLC and ^1H NMR) by recrystallization from ethanol or short column chromatography afforded pure products (**12—14**).

12 (1.12 g, 94%): colorless needles; mp 82.5—83.5 °C; IR (KBr) 2900, 1700, 1580, 1480, 1420, 1350, 1300, 1220, 1160, 1110, 1020, and 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.57 (s, 3H), 2.00—2.50 (m, 4H), 2.62 (s, 3H), 5.97—7.00 (m, 4H), and 11.00 (br, 1H). Calcd for $C_{12}H_{15}NO_2S$: C, 60.73; H, 6.37; N, 5.90%. Found: C, 60.30; H, 6.26; N, 5.75%.

13 (1.22 g, 92%): colorless oil; IR (neat) 2950, 1720, 1580, 1480, 1360, 1300, 1180, 1120, 1020, amd 740 cm^{-1}; ^1H NMR (CCl_4) δ=1.17 (t, 3H), 1.57 (s, 3H), 1.67—2.57 (m, 4H), 2.63 (s, 3H), 3.95 (q, 2H), and 5.90—6.83 (m, 4H). Calcd for $C_{14}H_{19}NO_2S$: C, 63.36; H, 7.22; N, 5.28%. Found: C, 63.18; H, 7.27; N, 5.31%.

14 (1.23 g, 99%): pale yellow oil; IR (neat) 2900, 1720, 1660, 1580, 1480, 1360, 1300, 1120, 1020, 910, and 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.50—1.83 (m, 11H), 2.70 (s, 3H), 4.76 (br, 1H), and 6.17—7.27 (m, 4H). Calcd for $C_{14}H_{19}NOS$: C, 67.43; H, 7.68; N, 5.62%. Found: C, 67.26; H, 7.29; N, 5.63%.

Benzothiazolination of Steroid Ketones 10 and 11. MABT (0.14 g, 1 mmol) was added to a solution of 4-androstene-3,17-dione (**10**) (0.29 g, 1 mmol) in dichloromethane (1 ml) and the mixture was refluxed for 48 h. After removal of the solvent under reduced pressure, the residual crystalline product which did not contain the other isomers (monitored by TLC, ^1H NMR and IR) was recrystallized from methanol to afford pure **15** as colorless plates (0.38 g, 93%): mp 191—192 °C; IR (KBr) 2950, 2900, 1740, 1590, 1480, 1450, 1400, 1300, 1210, 1120, 1030, 860, and 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.87 (s, 3H), 1.05 (s, 3H), 1.10—2.45 (m, 19H), 2.62 (s, 3H), 5.47 (bs, 1H), and 6.00—7.00 (m, 4H). Calcd for $C_{26}H_{33}NOS$: C, 76.61; H, 8.16; N, 3.44%. Found: C, 76.98; H, 8.04; N, 3.15%.

Benzothiazolination of progesterone (**11**) was carried out on a 1 mmol scale for 24 h according to standard procedure. Recrystallization of crude product which did not contain the other isomers (monitored by TLC, ^1H NMR, and IR) from ethanol afforded pure **16** as colorless needles (0.42 g, 97%): mp 203—204 °C; IR (KBr) 2950, 2870, 1710, 1580, 1480, 1450, 1360, 1310, 1110, 1030, and 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.63 (s, 3H), 1.03 (s, 3H), 1.13—2.03 (m, 20H), 2.07 (s, 3H), 2.63 (s, 3H), 5.47 (bs, 1H), and 6.03—7.00 (m, 4H). Calcd for $C_{28}H_{37}NOS$: C, 77.19; H, 8.56; N, 3.21%. Found: C, 76.98; H, 8.58; N, 3.09%.

Benzothiazolination of β-Hydroxy Ketones 19 and 20. Benzothiazolination of **19** and **20** was carried out on a 5 mmol scale for 72 h according to standard procedure. Purification of the crude products by short column chromatography afforded pure **17** and **18**.

17 (0.81 g, 48%): pale yellow oil; IR (neat) 3400, 2900, 2850, 1580, 1470, 1360, 1290, 1160, 1120, 1040, 1020, and 730 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.67—1.83 (m, 24H), 2.60 and 2.65 (ds, 3H), 2.97 (br, 1H), 4.00 (br, 1H), and 5.98—6.93 (m, 4H). Calcd for $C_{20}H_{33}NOS$: C, 71.59; H, 9.91; N, 4.17%. Found: C, 71.83; H, 9.69; N, 4.35%.

18 (0.29 g, 24%): colorless needles after recrystallization from ethanol; mp 83.5—84 °C; IR (KBr) 3350, 2950, 1580, 1470, 1370, 1330, 1300, 1260, 1170, 1100, 940, 790, and 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.33 (s, 6H), 1.57 (s, 3H), 2.12 (d, 2H), 2.69 (s, 3H), 3.10 (br, 1H), and 6.17—7.14 (m, 4H). Calcd for $C_{13}H_{19}NOS$: C, 65.78; H, 8.07; N, 5.90%. Found: C, 65.49; H, 8.02; N, 5.80%.

Hydrolysis of 3-Methylbenzothiazolines. Method A (General). Silver nitrate (1.02 g, 6 mmol) dissolved in water (10 ml) was added to a stirred solution of benzothiazoline **3** (4 mmol) in acetonitrile (60 ml) and 0.05 M phosphate buffer (pH 7) (12 ml). After 15 min at room temperature, additional silver nitrate (1.02 g, 6 mmol) dissolved in water (10 ml) was added. After another 20 min at room temperature, triethylamine (0.6 ml, 6 mmol) was added to neutralize the released acid (HNO_3) and stirring was continued for 5 min. Saturated aq. NaCl solution was added to the reaction mixture and filtered through Celite. The filtrate was extracted with ether and the extract was filtered through silica gel (Wakogel C-300). Removal of the solvent afforded almost pure aldehyde **1** that was free of MABT. Benzothiazoline **4** was similarly hydrolized, except that stirring was continued for 1 h at 45 °C after the addition of triethylamine, to afford almost pure ketone **2** that was free of MABT. Product yields are summarized in Tables 1 and 2. The compounds **17** and **18** were hydrolyzed by the similar method to benzothiazoline **4** to give the corresponding β-hydroxy ketones **19** (88%) and **20** (94%).

Method B. Mercury(II) chloride (1.63 g, 6 mmol) was added to a solution of benzothiazoline **3g** or **4e** (4 mmol) in 4:1 (v/v) acetonitrile-water (25 ml). The mixture was refluxed for 4 h and then cooled. After filtration to remove the precipitate, the aqueous solution was extracted with dichloromethane. The extract was dried with $MgSO_4$ and concentrated under reduced pressure to afford almost pure aldehyde **1g** (0.39 g, 93%) or ketone **2e** (0.45 g, 94%) as a colorless oil.

Method C. *N*-Bromosuccinimide (1.42 g, 8 mmol) was added to a suspension of benzothiazoline **3g** or **4e** (4 mmol)

in water (40 ml) and the mixture was stirred at room temperature for 10 min. After filtration, the filtrate was extracted with dichloromethane and the extract was dried with $MgSO_4$. Removal of the solvent under reduced pressure afforded almost pure aldehyde **1g** (0.39 g, 93%) or ketone **2e** (0.41 g, 86%).

Method D. Chloramine T (1.35 g, 4.8 mmol) was added to a solution of benzothiazoline **3g** (4 mmol) in ethanol (40 ml) and the mixture was stirred at room temperature for 1 h. After concentration of the mixture under reduced pressure, the residue was diluted with dichloromethane and washed thoroughly with water. The dichloromethane solution was dried with $MgSO_4$ and concentrated to give almost pure aldehyde **1g** (0.36 g, 85%). Benzothiazoline **4e** (0.97 g, 4 mmol) was similarly treated with Chloramine T (1.35 g, 4.8 mmol) for 24 h to give almost pure ketone **2e** (0.10 g, 21%).

Method E. Methyl fluorosulfate (0.55 g, 4.8 mmol) was added to a stirred solution of benzothiazoline **3g** or **4e** (4 mmol) in dichloromethane (16 ml) and stirring was continued at room temperature until no starting material remained (monitored with TLC; 18 h for **3g**, 24 h for **4e**). The excess reagent was quenched with ether (4 ml) for 30 min and the solvent was removed under reduced pressure. The residue was taken up in a mixture of 5% aq. K_2CO_3 solution (8 ml) and THF (10 ml) and the mixture was stirred at room temperature for 4 h. The solution was extracted with ether and the extract was washed with 5% aq. HCl, 5% aq. $NaHCO_3$, and saturated aq. NaCl solutions. It was then dried with $MgSO_4$. Concentration of the organic layer under reduced pressure afforded almost pure aldehyde **1g** (0.39 g, 92%) or ketone **2e** (0.46 g, 96%).

Identification of the carbonyl products obtained in these hydrolysis experiments was performed by spectroscopic (NMR, IR, and MS) methods. These spectral data were in satisfactory agreement with those of the corresponding authentic samples.

Preparation of 3-Methylbenzothiazolium Perchlorates 5; General Procedure. (A) From 3-Methylbenzothiazolines 3: Trityl perchlorate (3.43 g, 10 mmol) was added to a stirred solution of benzothiazoline **3** (10 mmol) in dry acetonitrile (10 ml). The mixture was warmed to 50—60 °C and continuously stirred for 30 min after the mixture became a complete solution. After cooling for 30 min at 0 °C, ether was added to completely precipitate product. The separated precipitate was collected by filtration and washed with dry ether to give crude product which was sufficiently pure to use directly in the next alkylation step. Recrystallization of crude products from methanol afforded pure salts as colorless needles. Product yields are summarized in Table 5.

(B) From Aldehyde 1 (One-Pot Reaction): MABT (1.39 g, 10 mmol) was added to a solution of aldehyde (10 mmol) in acetonitrile (10 ml) and the mixture was refluxed until the starting aldehyde disappeared (monitored with TLC; similar reaction times when compared to the benzothiazolination in ethanol were required). After cooling to room temperature, trityl perchlorate (6.86 g, 20 mmol) was added with stirring and warmed to 50—60 °C. The mixture was stirred for 10 min at the same temperature after the mixture became a complete solution and then stirred for 30 min at 0 °C. Ether was added to precipitate product completely and separated precipitate was collected by filtration and then washed with ether. The crude salt was decolorized in methanol with active charcoal and recrystallized from methanol to give pure **5** as colorless needles. Product yields are summarized in Table 5.

5a: mp 163.5—164.5 °C (decomp); IR (KBr) 2950, 1580, 1520, 1460, 1440, 1340, 1200, 1090, 760, and 620 cm^{-1}; ^1H NMR (DMSO-d_6) δ=0.97 (t, 3H), 1.17—2.17 (m, 4H), 3.43 (t, 2H), 4.13 (s, 3H), 7.67 (m, 2H), and 8.17 (m, 2H). Calcd for $C_{12}H_{16}NO_4SCl$: C, 47.14; H, 5.27; N, 4.58%. Found: C, 46.83; H, 5.11; N, 4.41%.

5b: mp 84.5—85 °C (decomp); IR (KBr) 2950, 1520, 1460, 1380, 1340, 1200, 1080, 760, and 620 cm^{-1}; ^1H NMR (DMSO-d_6) δ=0.67—2.17 (m, 14H), 3.87 (m, 1H), 4.33 (m, 3H), 7.83 (m, 2H), and 7.97 (m, 2H). Calcd for $C_{15}H_{22}NO_4SCl$: C, 51.79; H, 6.37; N, 4.03%. Found: C, 51.85; H, 6.31; N, 3.77%.

5c: mp 138.5—139 °C (decomp); IR (KBr) 2950, 1580, 1520, 1460, 1340, 1220, 1080, 820, 760, 720, and 620 cm^{-1}; ^1H NMR (DMSO-d_6) δ=1.48 (d, 6H), 3.83 (m, 1H), 4.17 (s, 3H), 7.67 (m, 2H), and 8.17 (m, 2H). Calcd for $C_{11}H_{14}NO_4SCl$: C, 45.29; H, 4.84; N, 4.80%. Found: C, 45.09; H, 4.73; N, 4.78%.

5d: mp 213—214 °C (decomp); IR (KBr) 1580, 1540, 1450, 1340, 1250, 1090, 760, 700, and 620 cm^{-1}; ^1H NMR (DMSO-d_6) δ=4.17 (s, 3H), 7.03 (m, 2H), 7.73 (m, 5H), and 8.27 (m, 2H). Calcd for $C_{14}H_{12}NO_4SCl$: C, 51.62; H, 3.71; N, 4.30%. Found: C, 51.43; H, 3.63; N, 4.06%.

5e: mp 216—217 °C (decomp); IR (KBr) 1590, 1480, 1470, 1400, 1240, 1090, 840, 700, and 620 cm^{-1}; ^1H NMR (DMSO-d_6) δ=4.20 (s, 3H), 7.75 (m, 6H), and 8.27 (m, 2H). Calcd for $C_{14}H_{11}NO_4SCl_2$: C, 46.68; H, 3.08; N, 3.89%. Found: C, 46.30; H, 3.42; N, 3.86%.

5f: mp 195—196 °C (decomp); IR (KBr) 1600, 1500, 1460, 1400, 1340, 1310, 1260, 1180, 1080, 830, 770, and 620 cm^{-1}; ^1H NMR (DMSO-d_6) δ=3.88 (s, 3H), 4.20 (s, 3H), 7.18 (m, 2H), 7.77 (m, 4H), and 8.23 (m, 2H). Calcd for $C_{15}H_{14}NO_5SCl$: C, 50.64; H, 3.97; N, 3.94%. Found: C, 50.83; H, 3.89; N, 3.68%.

5g: mp 173—174 °C (decomp); IR (KBr) 2950, 1580, 1520, 1450, 1300, 1200, 1080, 760, 700, and 620 cm^{-1}; ^1H NMR (DMSO-d_6) δ=2.00—2.83 (m, 6H), 3.83 (m, 1H), 4.27 (s, 3H), 5.77 (m, 2H), 7.72 (m, 2H), and 8.22 (m, 2H). Calcd for $C_{14}H_{16}NO_4SCl$: C, 50.99; H, 4.89; N, 4.25%. Found: C, 50.86; H, 4.76; N, 3.78%.

Alkylation of Benzothiazolium Salts 5 with Grignard or Organolithium Reagents; General Procedure. A solution of Grignard reagents (prepared from 20% excess of the corresponding bromide or chloride) in dry THF or ether (20 ml) was added dropwise to a stirred and cooled suspension at −78 °C of benzothiazolium salt **5** (4 mmol) in THF or ether (40 ml). The mixture was stirred for 30 min at −78 °C and allowed to warm to room temperature. After being stirred for 1 h at room temperature, the mixture was quenched by the addition of saturated aq. NH_4Cl solution. The aqueous mixture was extracted with ether and the extract was dried with $MgSO_4$. Concentration of the solution under reduced pressure to afford the crude products **4k**, **4n—s**, and **4u**. A 20% excess of butyllithium in hexane or a solution of nonynyllithium or phenylethynyllithium in THF (prepared by lithiation of 20% excess of 1,1-dibromo-1-nonene[14] or phenylacetylene with butyllithium) was similarly used in place of the Grignard reagents, giving **4k—m** and **4t**. Purification was carried out by short column chromatography for compounds **4p**, **4q**, and **4u** and by recrystallization from ethanol for compounds **4o**, **4r**, and **4s**. The other products were almost pure (monitored with TLC) without purification.

Product yields are summarized in Table 6.

4k: pale yellow oil; IR (neat) 2900, 1580, 1480, 1360, 1300, 1260, 1120, 1050, 1020, and 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.67—2.00 (m, 18H), 2.73 (s, 3H), and 5.83—6.97 (m, 4H). Calcd for $C_{16}H_{25}NS$: C, 72.95; H, 9.56; N, 5.32%. Found: C, 73.22; H, 9.77; N, 5.10%.

4l: pale yellow oil; IR (neat) 2900, 2850, 2200, 1580, 1470, 1340, 1290, 1120, 1020, and 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.53—2.30 (m, 24H), 2.93 (s, 3H), and 6.38—7.05 (m, 4H). Calcd for $C_{21}H_{31}NS$: C, 76.54; H, 9.48; N, 4.25%. Found: C, 76.71; H, 9.77; N, 4.11%.

4m: pale yellow oil; IR (neat) 2950, 2850, 2200, 1580, 1470, 1350, 1300, 1260, 1120, 1070, 1020, 740, and 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.57—2.33 (m, 9H), 2.75 (s, 3H), and 6.05—7.47 (m, 9H). Calcd for $C_{20}H_{21}NS$: C, 78.13; H, 6.88; N, 4.56%. Found: C, 78.17; H, 6.73; N, 4.04%.

4n: pale yellow oil; IR (neat) 2950, 1580, 1480, 1380, 1360, 1300, 1200, 1120, 1050, 1020, and 730 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.67—2.00 (m, 18H), 2.73 (s, 3H), and 5.83—6.97 (m, 4H). Calcd for $C_{16}H_{25}NS$: C, 72.95; H, 9.56; N, 5.32%. Found: C, 72.59; H, 9.58; N, 5.45%.

4o: colorless needles; mp 70.5—71 °C; IR (neat) 2900, 1580, 1480, 1440, 1360, 1300, 1220, 1100, 1040, 1020, 730, and 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.67—1.67 (m, 9H), 2.58 (s, 3H), and 6.40—7.60 (m, 9H). Calcd for $C_{18}H_{21}NS$: C, 76.28; H, 7.47; N, 4.94%. Found: C, 76.11; H, 7.49; N, 4.74%.

4p: colorless oil; IR (neat) 2950, 1620, 1580, 1480, 1370, 1300, 1220, 1120, 1020, and 730 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.67—2.00 (m, 24H), 2.60 (s, 3H), and 5.67—6.83 (m, 4H). Calcd for $C_{19}H_{31}NS$: C, 72.95; H, 9.57; N, 5.32%. Found: C, 73.14; H, 9.91; N, 4.81%.

4q: colorless oil; IR (neat) 2950, 1580, 1480, 1360, 1300, 1220, 1120, 1020, and 730 cm^{-1}; ^1H NMR (CCl_4) δ=0.50—2.13 (m, 16H), 2.57 (s, 3H), and 5.67—6.77 (m, 4H). Calcd for $C_{15}H_{23}NS$: C, 72.23; H, 9.29; N, 5.62%. Found: C, 72.37; H, 9.59; N, 5.37%.

4r: colorless needles; mp 140—140.5 °C; IR (KBr) 1570, 1480, 1440, 1340, 1300, 1220, 1150, 1100, 1120, 980, 890, 730, and 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.55 (s, 3H) and 6.33—7.50 (m, 14H). Calcd for $C_{20}H_{17}NS$: C, 79.17; H, 5.65; N, 4.62%. Found: C, 79.66; H, 5.42; N, 4.35%.

4s: colorless needles; mp 98.5—99 °C; IR (KBr) 3100, 2950, 1580, 1480, 1440, 1370, 1300, 1220, 1180, 1120, 1050, 1020, 770, 740, and 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.62 (s, 3H), 3.53 (s, 2H), and 6.07—7.67 (m, 14H). Calcd for $C_{21}H_{19}NS$: C, 79.46; H, 6.03; N, 4.41%. Found: C, 78.84; H, 6.04; N, 4.16%.

4t: pale yellow oil; IR (neat) 2950, 1580, 1500, 1420, 1320, 1160, 1040, and 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.67—1.83 (m, 9H), 2.53 (s, 3H), 3.68 (s, 3H), and 6.37—7.50 (m, 8H). Calcd for $C_{19}H_{23}NOS$: C, 72.80; H, 7.40; N, 4.47%. Found: C, 72.66; H, 7.62; N, 4.82%.

4u: colorless oil; IR (neat) 2900, 1650, 1580, 1460, 1360, 1300, 1220, 1120, 1020, 960, 920, and 730 cm^{-1}; ^1H NMR (CCl_4) δ=0.67—2.23 (m, 16H), 2.64 (s, 3H), 5.47 (m, 2H), and 5.73—6.83 (m, 4H). Calcd for $C_{18}H_{25}NS$: C, 75.21; H, 8.77; N, 4.87%. Found: C, 75.69; H, 9.08; N, 4.61%.

3-Methylbenzothiazolium Iodide (6a). A solution of benzothiazole (1.1 g, 8 mmol) in DMF (3 ml) and iodomethane (3 ml, 48 mmol) was refluxed for 2 h. The mixture was diluted with ether and cooled in an ice bath to completely precipitate the product. The pale yellow needles obtained were collected by filtration and washed thoroughly with ether. Recrystallization of the crude product from methanol afforded pure **6a** as colorless needles (2.1 g, 95%): mp 217 °C (decomp); IR (KBr) 3000, 1580, 1520, 1450, 1400, 1370, 1110, 1030, 880, 750, and 695 cm^{-1}; ^1H NMR (DMSO-d_6) δ=4.33 (s, 3H), 7.75 (m, 2H), 8.28 (m, 2H), and 10.38 (s, 1H). Calcd for C_8H_8NSI: C, 34.67; H, 2.91; N, 5.05%. Found: C, 34.48; H, 2.83; N, 4.86%.

3-Methylbenzothiazolium Fluorosulfate (6b). Methyl fluorosulfate (3.42 g, 30 mmol) was added to a solution of benzothiazole (1.35 g, 10 mmol) in dichloromethane (10 ml) and the mixture was refluxed for 24 h. After cooling to room temperature and a similar workup as in the preparation of **6a**, recrystallization of crude product from methanol afforded pure **6b** (2.24 g, 90%): mp 107—108 °C (decomp); IR (KBr) 3450, 3050, 1720, 1620, 1580, 1520, 1440, 1400, 1280, 1080, 900, 880, 820, 760, and 580 cm^{-1}; ^1H NMR (DMSO-d_6) δ=4.35 (s, 3H), 7.72 (m, 2H), 8.27 (m, 2H), and 10.38 (s, 1H). Calcd for $C_8H_8NO_3S_2F$: C, 38.55; H, 3.23; N, 5.62%. Found: C, 38.46; H, 3.18; N, 5.61%.

3-Methylbenzothiazolium Methyl Sulfate (6c). Benzothiazole (1.35 g, 10 mmol) was methylated for 72 h with dimethyl sulfate (3.78 g, 30 mmol) in dichloromethane (10 ml) by the same procedure for **6b**. Recrystallization of crude product from methanol afforded pure **6c** (0.42 g, 16%): mp 122—124 °C (decomp); IR (KBr) 3450, 3050, 1610, 1580, 1520, 1440, 1400, 1280, 1250, 1210, 1060, 1020, 900, 760, 720, and 570 cm^{-1}; ^1H NMR (DMSO-d_6) δ=3.32 (s, 3H), 4.33 (s, 3H), 7.72 (m, 2H), 8.25 (m, 2H), and 10.33 (s, 1H). Calcd for $C_9H_{11}NO_4S_2$: C, 41.37; H, 4.24; N, 5.36%. Found: C, 40.92; H, 4.10; N, 5.26%.

3-Methylbenzothiazolium Tetrafluoroborate (6d). Trimethyloxonium tetrafluoroborate (1.63 g, 10 mmol) was added in portions to a solution of benzothiazole (1.35 g, 10 mmol) in dichloromethane (10 ml). After the reaction mixture was refluxed for 20 min, the solvent was removed by evaporation under reduced pressure. The residual sirup was crystallized from acetone-dichloromethane-ether to give the crude product as colorless needles. Recrystallization from acetone-dichloromethane afforded pure **6d** as colorless needles (2.26 g, 95%): mp 118.5—119.5 °C (decomp); IR (KBr) 3050, 1580, 1520, 1440, 1400, 1370, 1320, 1280, 1080, 900, 760, 720, 570, and 520 cm^{-1}; ^1H NMR (DMSO-d_6) δ=4.37 (s, 3H), 7.73 (m, 2H), 8.23 (m, 2H), and 10.33 (s, 1H). Calcd for $C_8H_8NSBF_4$: C, 40.54; H, 3.40; N, 5.91%. Found: C, 40.42; H, 3.19; N, 5.88%.

Alkylation of 3-Methylbenzothiazolium Salts 6. Benzothiazolium salts **6a—d** (4 mmol) were allowed to react with 1.2 equiv of organometallic reagent according to standard procedure for the alkylation of the salt **5**, giving **3a**, **3g**, **3i**, and **3m—o**. In the case of **3a** obtained in the reaction of **6a** with butylmagnesium bromide, purification by short column chromatography was carried out to give pure **3a** as pale yellow oil. The other products were almost pure (monitored with TLC) without purification. Product yields are summarized in Table 7.

3m: pale yellow oil; IR (neat) 3050, 2900, 2850, 1640, 1580, 1480, 1370, 1330, 1300, 1120, 1020, 920, and 740 cm^{-1}; ^1H NMR (CCl_4) δ=2.50 (t, 2H), 2.68 (s, 3H), 4.67—5.17 (m, 3H), 5.50 (m, 1H), and 5.87—6.83 (m, 4H). Calcd for $C_{11}H_{13}NS$: C, 69.06; H, 6.85; N, 7.32%. Found: C, 69.29; H, 6.83; N, 7.38%.

3n: pale yellow oil; IR (neat) 3050, 2800, 1950, 1680, 1580, 1480, 1370, 1330, 1290, 1120, 1020, 1000, 920, and 740 cm^{-1};

^{1}H NMR ($CDCl_3$) δ=1.05 (d, 3H), 2.74 (s, 3H), 5.06 (m, 3H), and 6.21—7.25 (m, 4H). This compound is slightly unstable in air.

3o: pale yellow oil; IR (neat) 2200, 1670, 1580, 1470, 1420, 1350, 1320, 1280, 1100, 1020, 740, and 690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=3.13 (s, 3H), 6.00—7.50 (m, 9H), and 7.93 (s, 1H). This compound is slightly unstable in air.

Benzothiazole-2-*d* (22). A stirred solution of benzothiazole (6.0 g, 45 mmol) in dry THF (90 ml) under nitrogen was cooled to −78 °C and 20% excess of butyllithium in hexane (1.6 M solution) was added dropwise. 2-Lithiobenzothiazole was immediately formed. This orange-colored anion solution was quickly quenched at −78 °C with D_2O (4.5 ml) after the addition of butyllithium. The mixture was allowed to warm to room temperature and diluted with water. The aqueous mixture was extracted with ether. The ether extract was dried with $MgSO_4$. Removal of the solvent under reduced pressure afforded almost pure **22** as a pale yellow oil (5.85 g, 95%; >98% deuteration by ^{1}H NMR): bp 73 °C/2 mmHg (1 mmHg≈133.322 Pa); ^{1}H NMR (CCl_4) δ=6.50—7.50 (m, 4H).

2-Deuterio-3-methylbenzothiazolium Iodide (23). Benzothiazole-2-*d* (**22**) (4.1 g, 30 mmol) was methylated with iodomethane (11.2 ml, 180 mmol) in DMF (16.8 ml) according to the procedure for the preparation of **6a**. Recrystallization of crude product from methanol afforded pure **23** as colorless needles (7.8 g, 94%): mp 217 °C (decomp); ^{1}H NMR (DMSO-d_6) δ=4.33 (s, 3H), 7.75 (m, 2H), and 8.23 (m, 2H).

3-Methyl-2-phenylbenzothiazoline-2-*d* (24). Benzothiazolium salt **23** (7.23 g, 26 mmol) was alkylated with phenylmagnesium bromide (1.2 eq) in THF according to standard procedure described previously. Recrystallization of the crude product as pale yellow needles from ethanol afforded pure **24** as colorless needles (4.7 g, 80%; >98% deuteration by ^{1}H NMR): mp 113 °C; ^{1}H NMR ($CDCl_3$) δ=2.58 (s, 3H) and 6.17—7.67 (m, 9H).

Benzaldehyde-2-*d*. Benzothiazoline **24** (4.6 g, 20 mmol) was hydrolyzed by Method A to afford almost pure benzaldehyde-*d* as a colorless oil (1.99 g, 94%; >98% deuteration by ^{1}H NMR): bp 72.5 °C/20 mmHg; ^{1}H NMR (CCl_4) δ=7.30—7.87 (m, 5H).

References

1) J. F. W. McOmie, "Protective Groups in Organic Chemistry," Plenum Press, London (1973); T. W. Green, "Protective Groups in Organic Synthesis," Wiley, New York(1981).

2) Recently convenient and chemoselective acetalization and thioacetalization methods using alumina or silica gel have been reported: Y. Kamitori, M. Hojo, R. Masuda, and T. Yoshida, *Tetrahedron Lett.*, **26**, 4767 (1985); Y. Kamitori, M. Hojo, R. Masuda, T. Kimura, and T. Yoshida, *J. Org. Chem.*, **51**, 1427 (1986).

3) J. W. Ralls and B. Riegel, *J. Am. Chem. Soc.*, **76**, 4479 (1954); J. R. Williams and G. M. Sarkisian, *Synthesis*, **1974**, 32; D. A. Evans, L. K. Truesdale, K. G. Grimm, and S. L. Nesbitt, *J. Am. Chem. Soc.*, **99**, 5009 (1977).

4) Pure *cis*-2-acetonylcyclohexanecarbaldehyde have been obtained from the corresponding pure *cis*-benzothiazoline derivative with no trace of the corresponding and more stable *trans*-aldehyde: E. J. Corey and D. L. Boger, *Tetrahedron Lett.*, **1978**, 9.

5) The cleavage of 2-(α-hydroxyalkyl)benzothiazolines with Method A causes no dehydration to produce the corresponding α-hydroxy carbonyl compounds in good yields: H. Chikashita and K. Itoh, *Heterocycles*, **23**, 295 (1985); H. Chikashita, M. Ishibaba, K. Ori, and K. Itoh, *Bull. Chem. Soc. Jpn.*, **61**, 3637 (1988).

6) E. J. Corey and S. W. Walinsky, *J. Am. Chem. Soc.*, **94**, 8932 (1972).

7) B. T. Grobel, A. Wijsman, and A. Van der Gen, *J. Org. Chem.*, **44**, 1847 (1979).

8) I. Degani and R. Fochi, *J. Chem. Soc., Perkin Trans. 1*, **1976**, 1886.

9) G. Picotin and P. Miginiac, *J. Org. Chem.*, **50**, 1299 (1985).

10) I. Degani, R. Fochi, and V. Regondi, *Tetrahedron Lett.*, **22**, 1821 (1981).

11) J. Nakayama, *Bull. Chem. Soc. Jpn.*, **55**, 2289 (1982).

12) V. S. Huning, D. Scheutzow, H. Schlaf, and H. Quast, *Justus Liebigs Ann. Chem.*, **765**, 113 (1972).

13) J. Dauben, Jr., L. R. Honnen, and K. M. Harmon, *J. Org. Chem.*, **25**, 1442 (1960).

14) E. J. Corey and P. L. Fuchs, *Tetrahedron Lett.*, **1972**, 3769.