KETONE-GENERATING REACTION OF 3-METHYL-2-(1'-HYDROXYDIALKYL-METHYL)BENZOTHIAZOLIUM IODIDE UNDER BASIC CONDITIONS

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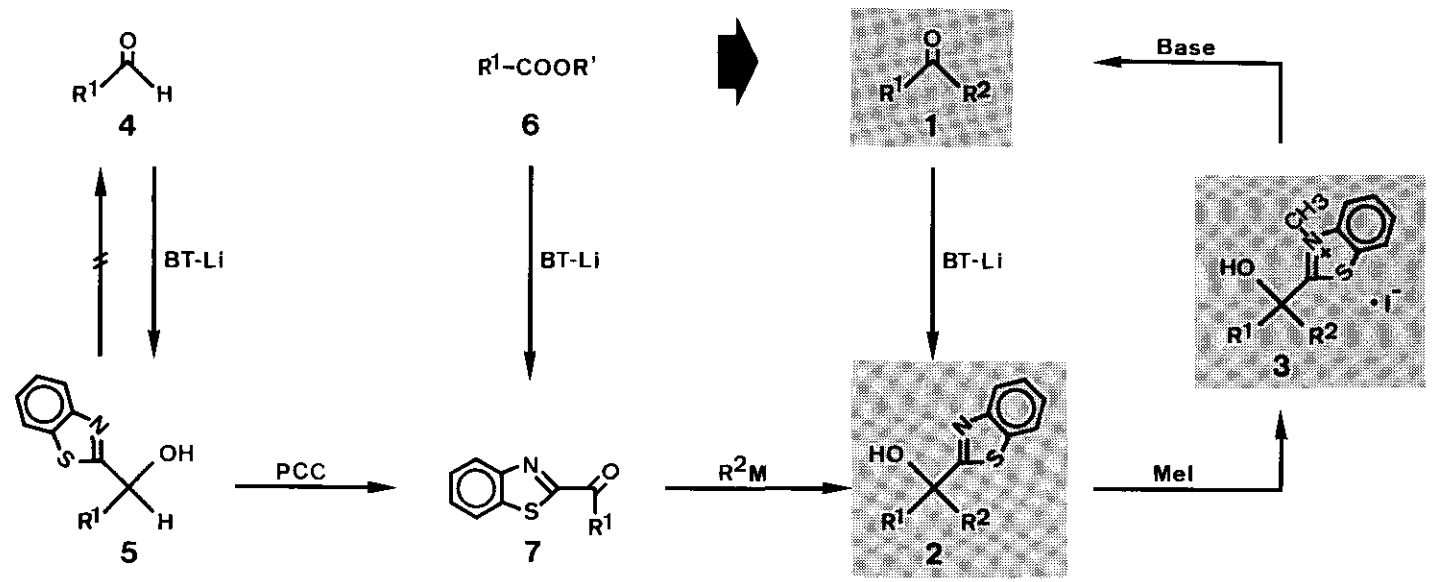
Abstract ——— Quaternized benzothiazol-2-yl moiety was found to be a good leaving group in the ketone-generating reaction of 3-methyl-2-(1'-hydroxydialkylmethyl)benzothiazolium iodides. The benzothiazolium salts easily obtained from ketones via methylation of 2-(1'-hydroxydialkylmethyl)benzothiazoles with methyl iodide, produced the corresponding ketones in excellent yields by the treatment with a variety of bases. Aldehydes and carboxylic esters were convertible to ketones by using the present methodology.

Benzothiazole ring system (hereafter denoted as BT) is of increasing importance as synthetically useful units.[1-3] Recently, our reports disclosed the usefulness of 2,3-dihydro-2-phenyl BT as a selective reducing agent in the conjugate reduction of α,β-unsaturated carbonyl compounds[2] and of BT as a masked carbonyl function in the synthesis of α-hydroxy-carbonyl compounds.[3] During our investigation to explore further synthetic utility of BT, easily obtainable 3-methyl-2-(1'-hydroxydialkylmethyl)benzothiazolium salts (3) were found to be convertible to the corresponding ketones (1) by mild basic treatment. In this paper, we would like to report a new type of ketone-generating reaction including a unique carbon-carbon bond fission by the use of BT as a leaving unit.

As outlined in Scheme 1, the present methodology comprises the preparation of 2-(1'-hydroxydialkylmethyl)benzothiazoles (2) via a carbon-carbon bond formation between BT and carbonyl compounds (1 and 4) or carboxylic esters (6), and the subsequent quaternization of 2 with methyl iodide leading to the corresponding salts (3), followed by the base-catalyzed cleavage of 3.



Stability of α-hydroxy BT(2)[a]

Reaction conditions	Recovery/%[b]
1 N-KOH / CH_3OH / 70 °C / 7 h	96
20%-H_2SO_4 / 70 °C / 7 h	96
H_2 / 5% Pd-C / C_2H_5OH / 1 atom / r.t. / 18 h	94
$NaBH_4$ / C_2H_5OH / r.t. / 24 h	99
CF_3COOH / r.t. / 24 h	98
Al_2O_3 / CH_3OH / reflux / 10 h	97

a) Checked with 2 (R^1: Me, R^2: Ph)
b) Isolated yield

Locked Protection

2 : Locked Form

MeI : Key

3 : Delocked Form

1 : Opened Form

Scheme 1

The transformation of carbonyl compounds (1 and 4) into the respective α-hydroxy BTs (2 and 5) was achieved by the reaction with 2-lithio BT in THF at -78°C. As previously mentioned,[3] a variety of carbonyl compounds afforded the adducts (2 and 5) in good yields. Furthermore, 5 was found to be convertible into 2 by the pyridinium chlorochromate (PCC) oxidation (e.g. R^1 = Ph; 88% yield) followed by alkylation with alkyllithium or Grignard reagents.

We have found that 2 can be also prepared from carboxylic esters (6) via acylation of BT. When 2-lithio BT was treated with 1.1 equiv of 6 in THF at -78°C to room temperature, 2-acyl BTs (7) was obtained in good yields (Table 1). Thus obtained 7 was reacted with 1.1 equiv of alkyllithium or Grignard reagent to give 2 in excellent yields (Table 1). These reactions could be carried out in one-pot fashion by employing 2.0 equiv of alkylating reagent (e.g. R^1 = Et, R^2M = n-BuLi; 67% yield).

Table 1. Preparation of the α-hydroxy BTs (2) from carboxylic esters (6)

R^1	R	R^2M	Yield of 7/%*	Yield of 2/%*
Ph	Et	n-BuLi	76	92
Ph	—	n-BuMgBr	—	91
Et	Et	n-BuLi	68	83
n-pentyl	Et	n-BuLi	63	85
i-Pr	Et	n-BuLi	64	73
t-Bu	Me	n-BuLi	69	46

* Yield of isolated, pure product.

For generation of ketones from 2, activation step of 2 is required. This was performed by quaternization of 2 to 3 with methyl iodide in DMF, and most of these methylations proceeded in good yields as described previously (more than 70%).[3] The progress of the reaction for the generation of the ketones (1) from the salts (3) under basic conditions was monitored by using the salt (3a; R^1 = Me, R^2 = Ph) as a representative (Table 2). We found that 3a could be easily converted to acetophenone by stirring the two-layers mixture consisting of the salt, n-hexane and excess of 10% aq. K_2CO_3 (Method-A) which could be replaced by excess of 10% aq. NaOAc (Method-C). The homogeneous reaction in ethanol with excess of 10% aq. K_2CO_3 (Method-B) was also effective to give acetophenone in nearly quantitative yield. On the other hand, organic bases such as 1,8-diazabicyclo[5.4.0]undec-7-ene

Table 2. Conversion of 3a into acetophenone

Method	Base (eq)	Solvent	Temp./°C	Time/h	Yield/%[a]
A	K_2CO_3 (1.5)	H_2O/ n-hexane	60	2	95
B	K_2CO_3 (1.5)	H_2O/ ethanol	reflux	7	92
C	NaOAc (3.0)	H_2O/ n-hexane	60	2	91
D	DBU (1.0)	ethanol	r.t.	2	86
E	DBU (0.2)	ethanol	reflux	2	90
F	TEA (1.0)	ethanol	r.t.	2	89
G	none	90%-aq.ethanol	reflux	3 days	77[b]

a) Isolated yield. b) 3-Methylbenzothiazolium iodide was isolated in 83% yield.

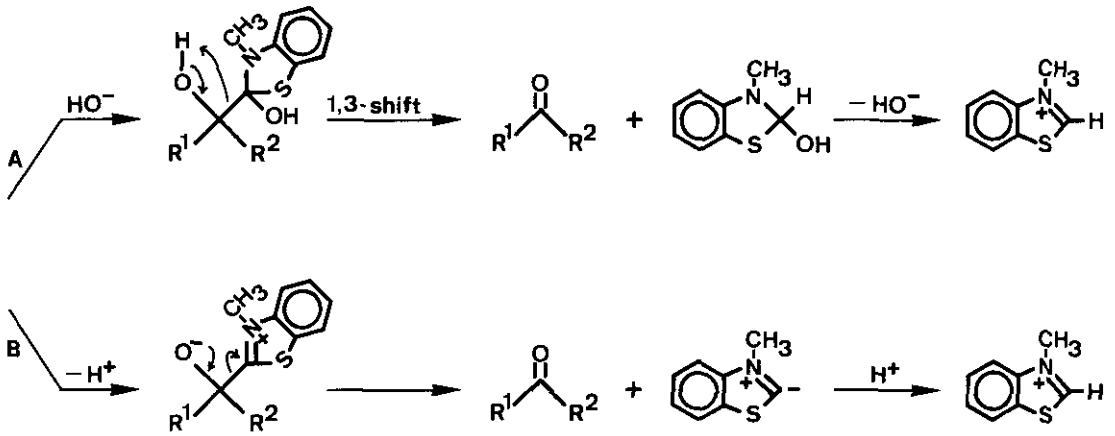
(DBU) or triethylamine (TEA) were effective in place of inorganic bases. Thus, the treatment of 3a with 1.0 equiv of DBU or TEA in ethanol at room temperature (Method-D, F), or the treatment with catalytic amount (0.2 equiv) of DBU in the same solvent under reflux temperature (Method-E), gave acetophenone in good yield. In these conditions, Method-A is the most clean, and evapolation of the organic layer gave almost pure acetophenone. Furthermore, this acetophenone-generating reaction proceeded in 90% aq. ethanol without base by prolonged refluxing (Method-G) and, in this case, 3-methylbenzothiazolium iodide produced could be isolated from the reaction mixture. As shown in Table 3, other benzothiazolium salts (3) having a variety of substituent were also cleaved smoothly under the conditions of Method-A, and the corresponding ketones (1) were obtained in quantitative yields.

Table 3. Preparation of ketones (1) from the salts (3) by Method-A[a]

Entry	Thiazolium salt	R^1	R^2	Yield/%[b]
1	3b	CH_3	C_6H_5	95
2	3c	CH_3	C_6H_5	94
3	3d	CH_3	n-propyl	94
4	3e	CH_3	2-furyl	95
5	3f	$-(CH_2)_5-$		40
6	3g	$-(CH_2)_{11}-$		95
7	3h	C_6H_5	(E)-C_6H_5CH=CH-	0

a) Reaction conditions: 3, 4.0 mmol; 10%-aq.K_2CO_3, 8 ml; n-hexane, 4 ml; 60°C; 2 h. b) Isolated yield.

However, cleavage of 3-methyl-2-(1'-hydroxy-1',3'-diphenylprop-2'-en-1'-yl) benzothiazolium iodide (3h) to chalcone by the present methods was unexpectedly unsuccessful. Furthermore it should be noted that the cleavage of methiodide of 5 by the methods employed for cleavage of 3a produced the corresponding aldehydes in very low yields. This unsuccessful result is probably due to the complex equilibrium derived from so-called "active aldehyde" molecule which seems to be easily produced by proton abstraction of methiodide of 5 by the base.[4]
From the fact that the BT counterpart was successfuly isolated from the reaction mixture, two possible reaction mechanisms for the present cleaving reaction are proposed as illustrated in Scheme 2. Aldehyde-generating or related reactions of "active aldehyde" have been studied in connection with study on mechanism of thiamine pyrophosphate-catalyzed reactions.[4] In such reactions, the mechanism involved the formation of a ylide by carbon-carbon bond fission at 2-position of thiazole derivatives has been widely accepted. Therefor, we believe the present cleaving reaction to proceed by Mechanism-B.



Scheme 2

BT can be regarded to be a masked carbonyl function because BT nucleus can be easily converted into carbonyl group via benzothiazoline nucleus.[1c,3] On the other hand, the present form (2) can be considered to be a protected form for ketones since the parent ketones (1) of 2 are regenerated via the activated form (3) and 2 almost survived under the severe conditions commonly required for removal of other protecting groups (Scheme 1). This type of protection requiring activation step for deprotection is a new method in organic synthesis and called

"locked protection" (Scheme 1) which was recently named by Ohta et al.[5] Therefor the present methodology provides a different and useful route to prepare ketones by the use of BT.

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

REFERENCES AND NOTES

1. a) V. Calo, L. Lopez, and P. E. Todesco, J. Chem. Soc., Perkin Trans. I, 1972, 1652; b) F. Souto-Bachiller, G. S. Bates, and S. Masamune, J. Chem. Soc., Chem. Commun., 1976, 719; c) E. J. Corey and D. L. Boger, Tetrahedron Lett., 1978, 5; d) E. J. Corey and D. L. Boger, ibid., 1978, 9; e) T. Mukaiyama, Angew. Chem. Int. Ed. Engl., 1979, 18, 707.
2. H. Chikashita, M. Miyazaki, and K. Itoh, Synthesis, 1984, 308.
3. H. Chikashita and K. Itoh, Heterocycles, 1985, 23, 295.
4. R. B. Breslow, J. Am. Chem. Soc., 1958, 80, 3719; J. C. Sheehan and T. Hara, J. Org. Chem., 1974, 39, 1196; W. H. Rastetter, J. Adams, J. W. Frost, L. J. Nummy, J. E. Frommer, and K. B. Roberts, J. Am. Chem. Soc., 1979, 101, 2752; and references cited therein.
5. S. Ohta, S. Hayakawa, K. Nishimura, and M. Okamoto, Tetrahedron Lett., 1984, 25, 3251.

Received, 5th June, 1985