3-METHYLBENZOTHIAZOLINES AS A NEW PROTECTED FORM FOR THE CARBONYL FUNCTION

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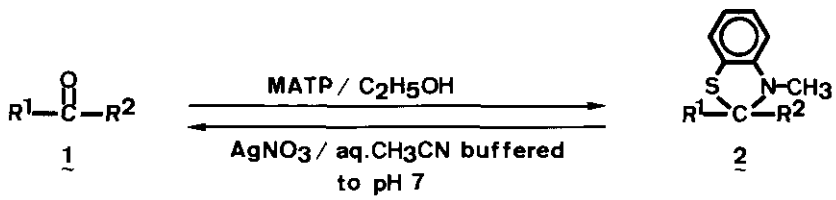
Abstract ——— Protection of carbonyl groups with N-methyl-o-aminothiophenol in ethanol under neutral conditions gave the corresponding benzothiazoline derivatives which were stable against basic, acidic and other reaction conditions. Removal of the protecting group was also performed under neutral conditions by using $AgNO_3$ or $HgCl_2$ in aqueous acetonitrile to regenerate the parent carbonyl compounds.

The acetal and ketal groups are the most widely used protecting groups for aldehydes and ketones.[1] Most of acetalization and ketalization are usually performed in the presence of various acidic catalysts. On the other hand, these forms have been well known to be very stable under besic conditions while they can be easily deprotected by treating with acid. However, this simplicity for cleavage is disadvantageous at the same time because such compounds can not be treated with acid except for removing the protection. During the course of various synthetic projects, the following situations may occur; a) the carbonyl group must be protected or deprotected under neutral conditions in the case of the synthesis for acid-sensitive molecules or intermediates, b) the protected form must be treated under acidic conditions, so that it is important from a synthetic viewpoint to find acid-resistant protected form for carbonyl groups which is readily prepared and deprotected under neutral conditions.

We now wish to report a useful new type of protection of aldehydes and ketones by conversion to 3-methylbenzothiazoline derivatives. This method allows efficient protection and deprotection under neutral conditions, and affords protection of carbonyl group against various basic and acidic conditions.

The preparation of the reagent required for protection step, N-methyl-o-amino-thiophenol (MATP), was conveniently accomplished by the reductive ring-opening reaction of commercially available benzothiazole with lithium aluminum hydride in THF under refluxing (78% yield; bp 84°C/ 2 mmHg). Conversion of carbonyl compounds to the corresponding benzothiazoline derivatives was effected by refluxing the solution of MATP and carbonyl compound in ethanol for the appropriate time. Table 1 summarizes some of the typical experimental results. Generally, this method could be applied efficiently to a variety of aldehydes and ketones to give the corresponding 2-substituted and 2,2-disubstituted 3-methylbenzothiazolines (2) in excellent yields respectively. However, the reaction of hindered ketone such as diisopropyl ketone with MATP hardly proceeded even under prolonged refluxing. Acyclic α,β-unsaturated carbonyl compounds were also much less reactive and their reactions with MATP under the present conditions gave the corresponding benzo-thiazolines in low yields. Furthermore, it should be noted that the reaction of ketones was generally more sluggish than that of aldehydes and required longer reaction time. This different reactivity for protection is advantageous from the synthetic point of view since it enables the selective protection of aldehydes in the presence of ketones. In fact, the treatment of ketoaldehyde (3c) with 1.0 equiv of MATP afforded the thiazoline (4c) in excellent yield with high selectivity. Table 2 shows the general levels of selective monothiazolination of a variety of dicarbonyl compounds by the present method. As seen in the successful conversion of ketocarboxylic acid (3a) and ketoester (3b) into the corresponding thiazolines (4a and 4b), the protection of keto group can be easily performed in the presence of carboxylic acid or ester functional group. On the other hand, in contrast to the thioketalization of steroid ketones,[2] the highly selective benzothiazolination of 4-androstene-3,17-dione (3d) and progesterone (3e) could be realized to give 4d and 4e respectively.

Hydrolysis of the 3-methylbenzothiazoline derivatives to the parent carbonyl compounds could be accomplished two ways; (A) treatment with $AgNO_3$ (3.0 equiv) in aq. CH_3CN buffered to a pH 7 followed by neutralization of the acid (HNO_3) released (1.0 equiv Et_3N) or (B) treatment with $HgCl_2$ (1.5 equiv) in aq. CH_3CN under refluxing. Yields obtained in the deprotection for two test substances by these methods were as follows: benzaldehyde, 95% (Method-A), 94% (Method-B); acetophenone, 90% (Method-A), 93% (Method-B). Notable in the case of Method-A is the fact that such mild conditions are employed for the hydrolysis that delicate



1 2

Table 1. Preparation and Hydrolysis of 3-Methylbenzothiazoline Derivatives

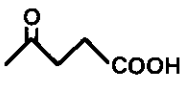
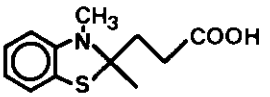
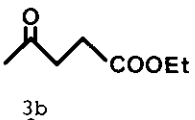
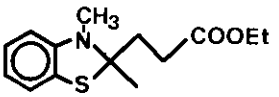
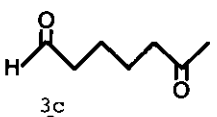
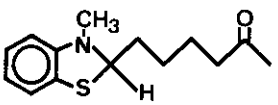
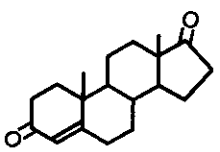
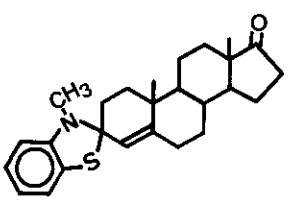
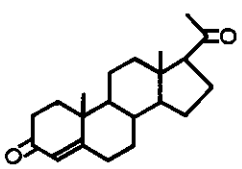
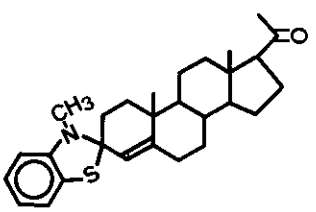
R^1	R^2	Thiazolination[a]		Hydrolysis[b]
		Time/h	Yield of 2/%[c]	Yield of 1/%[c]
$n\text{-}C_4H_9$	H	6	87	—
$n\text{-}C_9H_{19}$	H	24	82	86
$i\text{-}C_3H_7$	H	6	91	—
$CH_3(CH_2)_3(C_2H_5)CH$	H	24	84	83
$t\text{-}C_4H_9$	H	24	89	—
C_6H_5	H	6	80	95
cyclohexyl	H	6	90	94
3-cyclohexenyl	H	6	85	96
$(E)\text{-}C_6H_5CH{=}CH$	H	24	28	84
$(CH_3)_2C{=}CH(CH_2)_2CH(CH_3)CH_2$	H	24	85	93
$n\text{-}C_3H_7$	CH_3	10	88	—
$n\text{-}C_5H_{11}$	$n\text{-}C_5H_{11}$	24	90	94
$i\text{-}C_3H_7$	CH_3	24	91	—
$i\text{-}C_3H_7$	$i\text{-}C_3H_7$	24	trace	—
C_6H_5	CH_3	10	89	90
$-(CH_2)_5-$		4	97	92
$-CH{=}CH(CH_2)_3-$		24	69	92
$(E)\text{-}C_6H_5CH{=}CH$	CH_3	24	32	90
$(E)\text{-}C_6H_5CH{=}CH$	C_6H_5	24	21	98

a) Reaction conditions: MATP, 5 mmol; 1, 5 mmol; ethanol, 5 ml; reflux.

b) Reaction conditions: 2, 4 mmol; $AgNO_3$, 12 mmol; phosphate buffer (pH 7, 0.05 M), 12 ml; Et_3N, 4 mmol; $CH_3CN\text{-}H_2O$ (3:1 v/v), 80 ml; r.t., 40 min (for aldehyde); r.t. ~ 40°C, 100 min (for ketone).

c) Yield of isolated product.

Table 2. Selective Benzothiazolination of Dicarbonyl Compounds[a)]

Entry	Carbonyl Substrate	Product	Yield /%[b)]
1	 3a	 4a	94
2	 3b	 4b	92
3	 3c	 4c	99
4	 3d	 4d	93[c)]
5	 3e	 4e	97

a) Reaction conditions: substrate, 5 mmol; MATP, 5 mmol; ethanol, 5 ml; reflux; 24 h.

b) Yield of isolated product.

c) Reaction in CH_2Cl_2 under refluxing for 48 h.

Table 3. Stabilities of Benzothiazoline Derivatives

Reaction conditions	Recovery of 2/%*	
	R^1=Ph, R^2=H	R^1,R^2=n-Pr
$LiAlH_4$/ THF/ r.t./ 24 h	94	97
$NaBH_4$/ MeOH/ reflux/ 24 h	98	94
20% H_2SO_4/ 70°C/ 7 h	99	95
1N-KOH/ MeOH/ reflux/ 7 h	97	93
Al_2O_3/ MeOH/ reflux/ 24 h	93	97
CF_3COOH/ r.t./ 24 h	95	98
H_2/ 5% Pd-C/ EtOH/ 1 atom/ r.t./ 18 h	94	94

* Yield of isolated material.

centers[3] or functions[4] are unaffected. Further results for deprotection by employing Method-A are summarized in Table 1. In all cases examined, a variety of benzothiazolines (2) could be cleaved with no difficulties to give the corresponding carbonyl compounds in near quantitative yields.

Stabilities of 2 were checked by using 3-methyl-2-phenylbenzothiazoline and 3-methyl-2,2-dipropylbenzothiazoline as a sample. As shown in Table 3, both of these compounds almost survived under the severe conditions commonly required for removal of other protecting groups, and the resistibility to both of basic and acidic conditions adds some practically useful value to the present protection method. Further studies on the scope and limitations of the present method, as well as application to organic synthesis, are being undertaken in our laboratory.

REFERENCES AND NOTES

1. T. W. Green, "Protective Groups in Organic Synthesis", John Wiley & Sons, New York, 1981; J. F. W. McOmie, "Protective Groups in Organic Chemistry", Plenum Press, London, 1973.
2. J. W. Ralls and B. Riegel, J. Am. Chem. Soc., 1954, 76, 4479; J. R. Williams and G. M. Sarkisian, Synthesis, 1974, 32.
3. It has been reported that epimerizable centers are unaffected under this conditions (e.g., pure cis-2-acetonylcyclohexane-carboxaldehyde is obtained from the corresponding pure cis-benzothiazoline derivative with no trace of the corresponding more stable trans-aldehyde); E. J. Corey and D. L. Boger,

Tetrahedron Lett., 1978, 9.

4. We have previously demonstrated that the cleavage of α-hydroxybenzothiazolines by this mild method caused no dehydration to produce the corresponding α-hydroxy carbonyl compounds in good yields; H. Chikashita and K. Itoh, Heterocycles, 1985, 23, 295.

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