  Bull. Chem. Soc. Jpn., 63, 497—501 (1990)

Lewis Acid-Promoted Cross Aldol Reaction of Aldehydes with Ketones Utilizing 3-Methyl-2-phenyl-2-(2-oxoalkyl)benzothiazolines as an Enolate-Transferring Reagent

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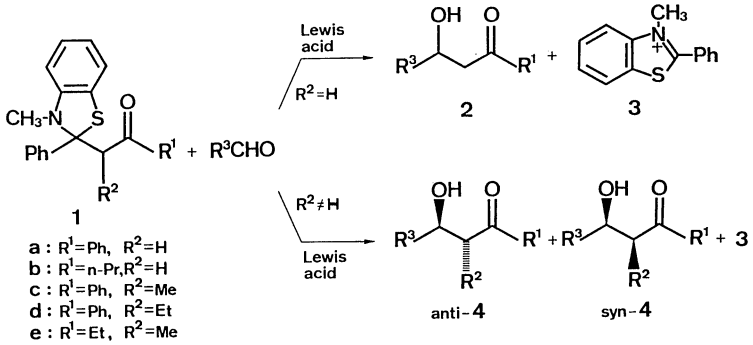
(Received October 6, 1989)

The treatment of a variety of 3-methyl-2-phenyl-2-(2-oxoalkyl)benzothiazolines with aldehydes in the presence of 2 equivalents of $SnCl_4$ in dichloromethane at −78 °C underwent a carbon–carbon bond cleavage at the 2-position of the benzothiazoline ring releasing an 2-oxoalkyl moiety followed by the concurrent aldol-type reaction with aldehydes to afford the corresponding β-hydroxy ketones. Among the Lewis acids examined, $SnCl_4$ was found to be most effective, while a similar reaction employing trimethylsilyl trifluoromethanesulfonate as an electrophilic promoter mainly gave the corresponding aldol-condensation product. In the case of the reaction with 3-methyl-2-phenyl-2-(1-substituted 2-oxoalkyl)benzothiazolines, a diastereomeric mixture of α-substituted β-hydroxy ketones as cross aldol products was obtained and the anti preference was generally observed for reactions with the benzothiazolines possessing an aromatic ketone moiety in modest to poor selectivity ranging between 69 : 31 and 57 : 43. In contrast to this, the reaction of the benzothiazoline possessing an alkyl ketone moiety, 3-methyl-2-phenyl-2-(1-methyl-2-oxobutyl)benzothiazoline, with benzaldehyde showed syn preference in modest selectivity of 70 : 30.

The aldol reaction is one of very important, fundamental, and useful reactions in organic synthesis and has been extensively investigated in recent years. Although various types of aldol reactions in aprotic solvents have been reported, most of reactions can be fundamentally classified into a group of reactions either with enolates possessing a Lewis acidic metal counterion or with a combination of enol silyl ethers and an appropriate electrophilic activator of carbonyls. We have recently shown that, under appropriate conditions, hydrogen at the C-2 position of 2-phenylbenzazolines can be nucleophilically transferred as a "hydride" to electrophilically activated α,β-unsaturated carbonyl compounds,[1] electron-deficient olefins,[1b,2] α-halo carbonyl compounds, and acid chlorides[3] to give the corresponding conjugate reduction and reductive dehalogenation products in high yields.[4] In a part of our attempts to extend this "hydride" transferring ability of the 2-phenylbenzazoline ring system to other anionic species, we have found that "enolate" can be also transferred successfully to an aldehyde under extremely mild conditions using a Lewis acid as an electrophilic promoter, allowing the realization of an enolate transfer-type aldol reaction.[5,6] In this paper, we wish to report details of a novel type of cross aldol reaction of aldehydes with ketones utilizing a combination of a variety of 3-methyl-2-phenyl-2-(2-oxoalkyl)benzothiazolines (**1**) as an enolate transferring reagent and a Lewis acid as an electrophilic promoter and disclose the scope of the reaction including its stereochemical aspects, limitations, and general applicability.[7]

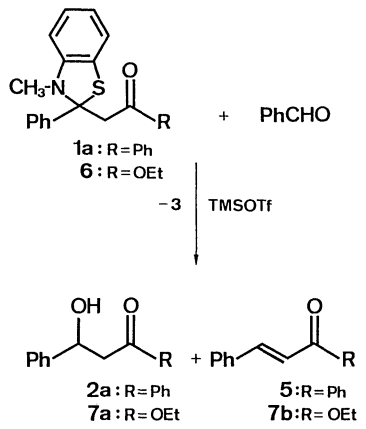
Results and Discussion

Initially, a survey of the enolate-transferring ability of the benzothiazolines **1** to aldehydes was conducted using the reaction of 3-methyl-2-phenacyl-2-phenylbenzothiazoline (**1a**) with 2 equivalents of benzaldehyde as a representative example (Table 1). Although any reaction of **1a** with benzaldehyde could not have occurred without an additive, Lewis acids were found to promote the reaction to afford the cross aldol product, 3-hydroxy-3-phenylpropiophenone (**2a**), with varying yields depending on the type of Lewis acid and reaction conditions. Among the reactions examined, the reaction employing 2 equivalents of $SnCl_4$ at −78 °C was the most effective (Entry 1) while the same reaction with 1 equivalent of $SnCl_4$ or



Scheme 1.

the reaction at −40 °C produced the aldol product **2a** in lower yield (Entries 2,3). $BF_3 \cdot OEt_2$ could also significantly promote the reaction while $ZnCl_2$ was almost ineffective (Entries 4,5). $TiCl_4$ is well known to be an efficient electrophilic activator for a carbonyl group and is now used commonly in a variety of synthetic reactions including aldol reactions.[8] However, the reaction with $TiCl_4$ mainly gave the aldol condensation product, chalcone (**5**), in 43% isolated yield together with the desired aldol product **2a** (11%) (Entry 6). This is probably due to the strong acidity of $TiCl_4$. Trimethylsilyl trifluoromethanesulfonate (TMSOTf) is also known as an efficient reagent for the electrophilic activation of the oxygen atom.[9] Using 2 equivalents of this reagent for a Lewis acid, we have carried out the reaction of **1a** with benzaldehyde in dichloromethane at −78 °C for 6 h (Scheme 2). Although the reagent could less effectively promote the reaction, this reaction led to the formation of the aldol product **2a** and the condensation product **5** in 19% and 16% yields, respectively. The reaction of **1a,b** with several different aldehydes was thus examined under the optimum conditions (2 equiv of $SnCl_4$, −78 °C). The results are summarized in Table 2. An aliphatic aldehyde, a hindered aldehyde, and an α,β-unsaturated aldehyde reacted with **1a** to give the corresponding aldol products **2b—d** without their dehydration products (Entries 2—4). It is noteworthy that the high preference for non-conjugate 1,2-addition (i.e., aldol reaction) to an α,β-unsaturated



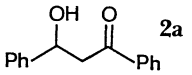
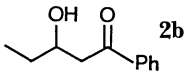
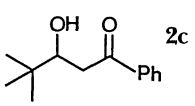
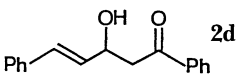
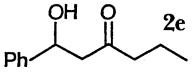
Scheme 2.

Table 1. Aldol-Type Reaction of Benzothiazoline **1a** with Benzaldehyde in Dichloromethane in the Presence of a Lewis Acid

Entry	Lewis acid	(Equiv)	Time/h	Temp/°C	Yield of **2a**/%[a]
1	$SnCl_4$	(2)	6	−78	67
2	$SnCl_4$	(1)	8	−78	44
3	$SnCl_4$	(2)	6	−40	60
4	$BF_3 \cdot OEt_2$	(2)	6	−78	61
5	$ZnCl_2$	(2)	6	−78	Trace[b]
6	$TiCl_4$	(2)	6	−78	11[c]

a) Yield of pure product after MPLC. b) THF was used as a solvent in place of dichloromethane. c) The condensation product **5** (chalcone) was obtained in 43% yield.

Table 2. Aldol-Type Reaction of Benzothiazolines **1a,b** with a Variety of Aldehydes in Dichloromethane in the Presence of $SnCl_4$ at −78 °C[a]

Entry	Reagent **1**	R^3CHO	Time/h	Product **2**	Yield /%[b]
1	**1a**	PhCHO	6	 **2a**	67
2	**1a**	EtCHO	12	 **2b**	54
3	**1a**	*t*-BuCHO	12	 **2c**	18
4	**1a**	PhCH=CHCHO	12	 **2d**	40
5	**1b**	PhCHO	6	 **2e**	43

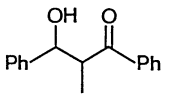
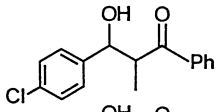
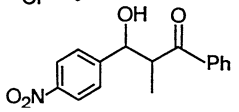
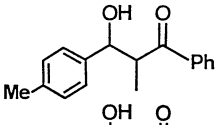
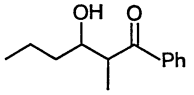
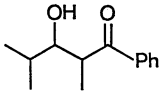
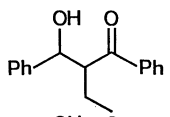
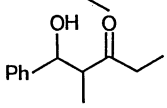
a) **1** : R^3CHO : $SnCl_4$=1 : 2 : 2 (molar ratio). b) Yield of pure product after MPLC.

aldehyde is in sharp contrast to the selective conjugate hydride addition to α,β-unsaturated carbonyl compounds using 2-phenylbenzazolines and $AlCl_3$.[1] As seen in the result of the reaction of **1b** with benzaldehyde giving the aldol product **2e**, the cross aldol reaction of an aliphatic ketone with an aldehyde proceeded successfully as well as in the case of an aromatic ketone (Entry 5).

The cross aldol reaction between two different ketones and the similar reaction of esters with aldehydes are also of importance in organic synthesis. Thus, we tried the reaction of **1a** with common ketones under the present reaction conditions but found that **1a** could not react with common ketones at all. Furthermore, we have examined the reaction of the benzothiazoline **6** possessing an ester moiety with benzaldehyde in the presence of TMSOTf or other Lewis acids under several different reaction conditions (Scheme 2). However, in all cases examined, the formation of the expected β-hydroxy ester **7a** or its dehydration product **7b** was not observed.

We next investigated the $SnCl_4$-promoted aldol reaction of aldehydes with a variety of 3-methyl-2-phenyl-2-(1-substituted 2-oxoalkyl)benzothiazolines (**1c—e**) (Scheme 1). All the compounds **1c—e** used were prepared as a respective single diastereoisomer by the procedure previously reported, although their relative stereochemistries have not been clarified.[10] The results of the aldol-type reaction are summarized in Table 3. In all cases, a diastereomeric mixture of anti and syn aldols **4a—h**[11] could be obtained without any appreciable amount of the condensation products. These results indicate that the present aldol-type reaction of ketones with aldehydes using **1** is fairly general and applicable to the synthesis of α-substituted β-hydroxy ketones as well as β-nonsubstituted ones. In the case of a series of reactions of the benzothiazoline **1c** possessing an aromatic ketone moiety with aromatic aldehydes, the anti preference was consistently observed in the selectivity ranging between 69:31 and 57:43 (Entries 1—4). The anti preference was also observed in the reaction of **1c** with an aliphatic aldehyde such as butanal and in the reaction of **1d** with benzaldehyde (Entries 5,7). In contrast to this, the reaction of **1c** with a relatively bulky aldehyde such as 2-methylpropanal and the cross aldol reaction of an

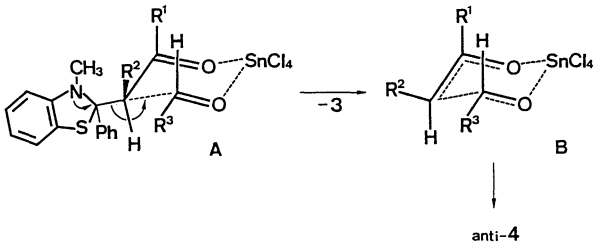
Table 3. Aldol-Type Reaction of Benzothiazolines **1c—e** with a Variety of Aldehyeds in Dichloromethane in the Presence of $SnCl_4$ at −78 °C[a]

Entry	Reagent **1**	R^3CHO	Product **4**	Yield /%[b]	Stereoselectivity[c] (*anti*-**4**:*syn*-**4**)[d]
1	**1c**	PhCHO	 **4a**	43	65:35
2	**1c**	p-ClPhCHO	 **4b**	52	69:31
3	**1c**	p-NO_2PhCHO	 **4c**	63	67:33
4	**1c**	p-MePhCHO	 **4d**	38	57:43
5	**1c**	n-PrCHO	 **4e**	52	53:47
6	**1c**	i-PrCHO	 **4f**	48	46:54
7	**1d**	PhCHO	 **4g**	18	51:49
8	**1e**	PhCHO	 **4h**	49	30:70

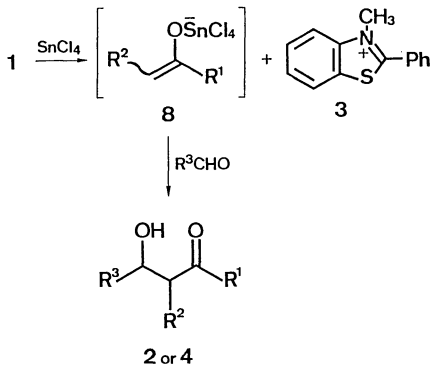
a) All the reactions were carried out for 6 h using the reagent system; **1**:R^3CHO:$SnCl_4$ =1:2:2 (molar ratio). b) Yield of pure diastereomeric mixture after MPLC. c) Determined by HPLC analyses. d) Stereochemistry was determined by ^1H NMR or ^{13}C NMR analyses.

aliphatic ketone with an aromatic aldehyde by using the reaction of **1e** with benzaldehyde exceptionally showed an opposite stereoselectivity giving *syn*-**4f** and *syn*-**4h** as major products in a low and modest selectivity of 54:46 and 70:30, respectively (Entries 6,8).

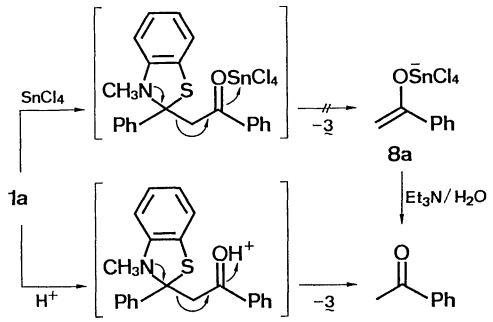
We have recently shown that the benzothiazolines **1** undergo a carbon-carbon bond cleavage to give the corresponding ketones via enole intermediates in high yields on treatment with a stoichiometric amounts of a protic acid in dichloromethane-methanol at room temperature (see Scheme 4).[12] If, in analogy to this reaction, the initial formation of enolates from **1** can easily proceed with the aid of $SnCl_4$, the common aldol pathway involving the reaction of tin enolates **8** with aldehydes should be operative in the present reaction (Scheme 3). In order to examine the possibility of this pathway, we have carried out the reaction of **1a** with 2 equivalents of $SnCl_4$ in dichloromethane at −78 °C followed by quenching with the addition of triethylamine and water (Scheme 4). However, this reaction did not produce significant amounts of acetophenone with **1a** being recovered almost unchanged. This result indicates that the tin enolate **8a** can not be formed efficiently by the reaction of **1a** with $SnCl_4$ when an aldehyde is absent in its reaction, and shows it to be rather unlikely that the aldol process occurred after completion of the formation of tin enolates **8** from **1** and $SnCl_4$ as shown in Scheme 3. Accordingly, we suggest that a synchronous mechanism (**A**) mediated by $SnCl_4$ leading to the usual six-membered chelating transition state (**B**) is more likely to operate in the reaction (Scheme 5); that is, we postulated that the enolate formation induced by leaving the 3-methyl-2-phenylbenzothiazolium moiety and the actual aldol process with an aldehyde occurred in either exact or nearly exact concurrence. This type of mechanism has already been reasonably proposed for the hydride-transfer reactions with 3-methyl-2-phenylbenzazolines and well conform to the driving force for the formation of the stable 3-methyl-2-phenylbenzothiazolium salts **3**.[1] In addition, the anti preference can be rationalized based on this mechanism because it is expected that the formation of the transition state **B** leading to anti aldols is more favorable than that of the transition state where R^2 is located at an axial position, although the exact explanation of the mechanism and its stereochemistry in the path from **A** to **B** seems to be difficult at present.



Scheme 5.



Scheme 3.



Scheme 4.

Experimental

IR spectra were recorded on a JASCO A-202 spectrophotometer. ^1H NMR spectra were measured with a JEOL PMX-60 spectrometer at 60 MHz using tetramethylsilane as an internal reference. HPLC analyses were performed on a Yanagimoto L-5000 high-pressure liquid chromatograph system using a reversed-phase column of Chemcosorb 7005H (4.6φ×300 mm).

Materials. Dichloromethane was freshly distilled over $CaCl_2$ before use. Lewis acids and trimethylsilyl trifluoromethanesulfonate were obtained as high-grade commercial products and used without purification. 3-Methyl-2-phenyl-2-(2-oxoalkyl)benzothiazolines (**1**) were prepared by the reaction of 3-methyl-2-phenylbenzothiazolium fluorosulfate with lithium enolates of ketones according to a previously reported method.[10]

General Procedure for the Aldol-Type Reaction of 3-Methyl-2-phenyl-2-(2-oxoalkyl)benzothiazolines (1) with Aldehydes. A solution of an aldehyde (4 mmol) in dry dichloromethane (5 ml) was cooled to −78 °C under a nitrogen atmosphere. To this solution, $SnCl_4$ (4 mmol) was added followed by the addition of benzothiazoline **1** (2 mmol). After stirring for an appropriate time (see Tables 1—3) at −78 °C, the reaction mixture was quenched by the addition of wet ether (10 ml) and then stirred for 30 min at −78 °C. The mixture was allowed to warm to room temperature and triethylamine (2 mmol) was then added. The mixture was stirred for another 10 min at room temperature and poured into ether (20 ml). After removing pre-

cipitated benzothiazolium salt **3** by filtration, the filtrate was thoroughly washed with water and the organic layer was dried over $MgSO_4$. The solution was concentrated under reduced pressure and the residue was subjected to MPLC (benzene–ethyl acetate, 9:1 v/v) to give pure β-hydroxy ketones **2** or a pure diastereomeric mixture of α-substituted β-hydroxy ketones **4**.

Identification of products was performed by spectroscopic (NMR and IR) methods. These spectral data were in satisfactory agreement with those of the corresponding authentic samples.

The diastereomer ratio of **4** was determined by HPLC analyses using the solvent system of methanol–water (7:3 v/v for **4a—c,f,g** or 6:4 v/v for **4d,e,h**).

The relative stereochemistry of the *anti*-**4** and *syn*-**4** was easily distinguished by ^1H NMR on the basis of the coupling constant between α and β protons ($J_{anti} > J_{syn}$)[13] or by ^{13}C NMR on the basis of the chemical shifts of the methyl carbon at the α-position ($\delta_{anti} > \delta_{syn}$).[14]

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