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NOVEL ALDOL-TYPE REACTION UTILIZING 3-METHYL-2-PHENYL-2-(2-OXOALKYL)BENZOTHIAZOLINE AS AN ENOLATE TRANSFERRING REAGENT

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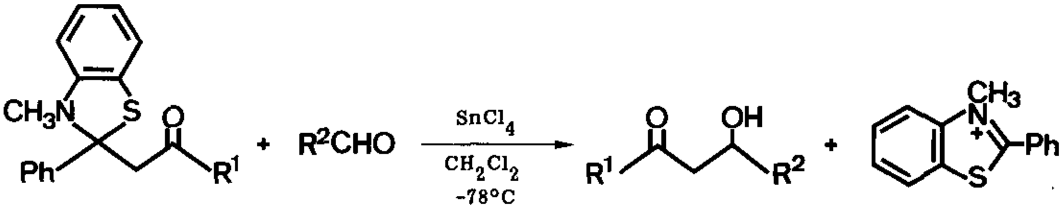
Abstract ——— An enolate transfer-type aldol reaction of the title benzothiazoline with aldehydes was successfully achieved in the presence of $SnCl_4$ to afford the cross aldol products.

The aldol reaction is one of the most important and fundamental reactions in organic synthesis and various aldol-type reactions in aprotic solvents have been extensively investigated. However, despite much work in this field, most of these reactions have been fundamentally achieved either with enolates possessing a Lewis acidic metal counterion or with a combination of enol silyl ethers and an electrophilic activator of carbonyls. In our attempts to extent the "hydride" transferring ability of 2-phenylbenzazoline ring system[1,2] to other anionic species, we have found that "enolate" can be also transferred effectively to electrophilically activated aldehydes under extremely mild conditions allowing the realization of enolate transfer-type aldol reaction.[3] In this paper, we report the novel aldol-type reaction utilizing 3-methyl-2-phenyl-2-(2-oxoalkyl)benzothiazoline (**1**) as an enolate transferring reagent.



1a : $R^1 = C_6H_5$
1b : $R^1 = n\text{-}C_3H_7$

2

3

We have found that 3-methyl-2-phenyl-2-(2-oxoalkyl)benzothiazolines are generally and easily obtained by the reaction of 3-methyl-2-phenylbenzothiazolium salts with lithium enolates in THF. Thus, 2-phenylbenzothiazolium fluorosulfonate was

Table 1. Aldol reaction of benzothiazoline (1) with aldehydes in the presence of Lewis Acid

Run	R^1	R^2	Lewis acid	(eq)	Time/h	Temp/°C	Yield of 2/% a)
1	C_6H_5	C_6H_5	$SnCl_4$	(1)	8	-78	44
2		C_6H_5	$SnCl_4$	(2)	6	-78	67
3		C_6H_5	$SnCl_4$	(2)	6	-40	60
4		C_6H_5	$BF_3\cdot O(C_2H_5)_2$	(2)	6	-78	61
5		C_6H_5	$TiCl_4$	(2)	6	-78	11 b)
6		C_6H_5	$ZnCl_2$	(2)	6	-78	trace c)
7		C_2H_5	$SnCl_4$	(2)	12	-78	54
8		$\underline{t}$-C_4H_9	$SnCl_4$	(2)	12	-78	18
9		PhCH=CH	$SnCl_4$	(2)	12	-78	40
10	$\underline{n}$-C_3H_7	C_6H_5	$SnCl_4$	(2)	6	-78	15

a) Yield of pure product isolated by column chromatography on silica gel.

b) Dehydration product (chalcone) was obtained in 43% yield.

c) Tetrahydrofuran was used as a solvent in place of dichloromethane.

alkylated (1 h at 0°C and then 1 h at room temperature) with 1 equiv. of the lithium enolates produced from acetophenone and 2-pentanone to give crystalline benzothiazolines (1a,b) in 71 and 69% yields, respectively. Initially, the reaction of benzothiazoline (1a) with benzaldehyde was carried out in dichloromethane in the presence of several Lewis acids. As shown in Table 1 (Runs 1-6), the reaction was most effectively accomplished at -78°C by the use of 2 equiv. of $SnCl_4$ to give the cross aldol product (3-hydroxy-3-phenylpropiophenone) together with a trace amount of acetophenone. Although $BF_3\cdot O(C_2H_5)_2$ could also be used satisfactorily, $ZnCl_2$ was ineffective. In these reactions, the cross aldol product was selectively obtained and no dehydration product, polycondensation product, or self-condensation product was formed. On the other hand, the reaction with $TiCl_4$ produced considerable amounts of dehydration product (chalcone: 43% yield) together with the aldol product (11% yield). $(CH_3)_3SiOTf$ which is well known as an efficient reagent for electrophilic activation of carbonyls, could less effectively promote the reaction (6 h at -78°C) to give the mixture of the aldol product (19% yield) and its dehydration product (16% yield). We next tried the reaction of benzothiazoline (1a) with several kinds of aldehydes under the optimum conditions (2 equiv. of $SnCl_4$, -78°C) (Table 1, Runs 7-9). Aliphatic aldehyde or even a hindered aldehyde reacted with benzothiazoline (1a) to give the desired aldol product in moderate yield with no trace of the corresponding dehydration product. When cinnamic aldehyde was employed, the aldol product (4-benzylidene-3-hydroxybutyrophenone) was selectively obtained in moderate yield. This shows the high preference of the present reaction for non-conjugate 1,2-addition to the α,β-unsaturated substrate and is in sharp contrast to $AlCl_3$-promoted "hydride" transfer reactions using 2-phenylbenzothiazolines or 2-phenylbenzimidazolines.[1] The enolate transferring ability of benzothiazoline (1b) derived from aliphatic ketone was similarly examined in the reaction with benzaldehyde (Run 10). This reaction led to the formation of the expected aldol product (1-hydroxy-1-phenyl-3-hexanone) although the yield was low (15% yield). Finally, it should be noted that the reaction of benzothiazoline (1) with ketones and the aldol-type reaction using benzothiazolines prepared from 2-phenylbenzothiazolium salt with ester enolates did not proceed under the present conditions.

A typical procedure for the aldol-type reaction of benzothiazoline (1) with aldehydes is as follows: a solution of aldehyde (4 mmol) in dichloromethane (5 ml) was cooled to -78°C and $SnCl_4$ (4 mmol) was added under nitrogen atmosphere followed by the subsequent addition of benzothiazoline (1) (2 mmol). After stirring was continued for an appropriate time (see Table 1) at -78°C, the reaction mixture was quenched with wet ether (10 ml) and allowed to warm to room temperature. Then triethylamine (2 mmol) was added and further stirred for 10 min at room temperature. The mixture was poured into ether and precipitated benzothiazolium salt (3) was removed by filtration. Work up followed by column chromatography over silica gel gave product (2).

Further studies on the scope, limitations, and mechanism of the present reaction are now in progress.

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