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erythro- OR *threo*-SELECTIVE ALDOL-TYPE REACTION VIA (*Z*)-*N*,*N*-DIMETHYL-*S*-TRIMETHYLSILYLKETENE *S*,*N*-ACETALS

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Summary

N,*N*-Dimethylthioamides can be converted stereoselectively into (*Z*)-*N*,*N*-dimethyl-*S*-trimethylsilylketene *S*,*N*-acetals, **2**. Condensation of **2** with benzaldehyde under the influence of a catalytic amount of tetrabutylammonium fluoride affords *erythro*-(R^*,R^*)-β-hydroxythioamides selectively in good yields. The aldol reaction is postulated to proceed via an acyclic transition state. Lewis acid-promoted condensation of **2** with benzaldehyde on the other hand affords mainly *threo*-(R^*,S^*)-β-hydroxythioamides when R^1 is not too bulky.

Introduction

The development of highly stereoselective aldol and related C–C bond forming reactions continue to be a dominant theme in synthetic organic chemistry [1a]. Most of them utilize enolate monoanions of a ketone, or an ester or their equivalent. In the presence of chelating counterions, a six-membered chair-like transition state has proven to be a very useful model [1b]. We established earlier that the enethiolate generated from *N*,*N*-dialkylthioamides $R^1CH_2CSN(R^2)_2$ provides *erythro*-aldol selectivity when $R^1 = CH_3$ or C_2H_5 and *threo*-aldol selectivity when $R^1 = CH(CH_3)_2$ [2]. At about the same time Tamaru et al. [3] noticed the same diastereoselectivity. More recently, several *erythro*-selective reactions have been developed with nucleophilically-activated naked enolates and unactivated carbonyl compounds [4]. We report here *erythro*-(R^*,R^*)-aldol condensation with quaternary ammonium enethiolates generated from (*Z*)-*N*,*N*-dimethyl-*S*-trimethylsilylketene *S*,*N*-acetals and *threo*-(R^*,S^*)-aldol selectivity mediated with a Lewis acid.

Structure of *N*,*N*-dimethyl-*S*-trimethylsilylketene *S*,*N*-acetals

The diastereoselectivity observed in aldol addition with lithium enethiolates [2,3] suggests that enethiolates derived from thioamides possess a *Z*-configuration in high

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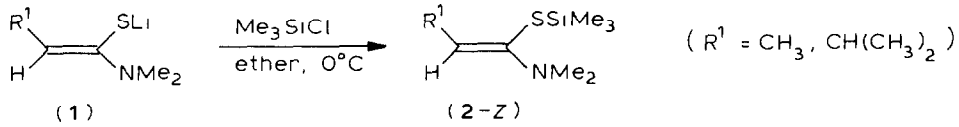
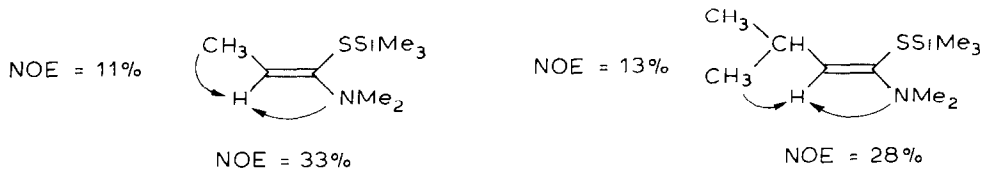
isomeric purity. Tamaru et al. [3,5] have reported the same reasoning against results reported previously [6] where the structure of ketene *S,N*-acetals was assigned an *E*-configuration by investigation of the chemical shifts of the vinylic proton in ^{1}H NMR spectra. Recently Narula [7] predicted by consideration of the $A^{(1-2)}$ and $A^{(1-3)}$-strain in the transition states for the deprotonation of amides and thioamides with LDA, the formation of *Z*-enolates on both kinetic and thermodynamic grounds. With ^{1}H NMR-NOE measurements we are now able to prove that *N,N*-dimethyl-*S*-silylketene *S,N*-acetals, generated from the corresponding lithium enethiolates, possess the *Z*-configuration:



(1) (2-*Z*)

The Nuclear Overhauser Effect (NOE) was employed in the structure determination [8], irradiation of $N(CH_3)_2$ and the protons of R^1 resulting in a positive enhancement to vinyl H, as shown in Scheme 1.



SCHEME 1

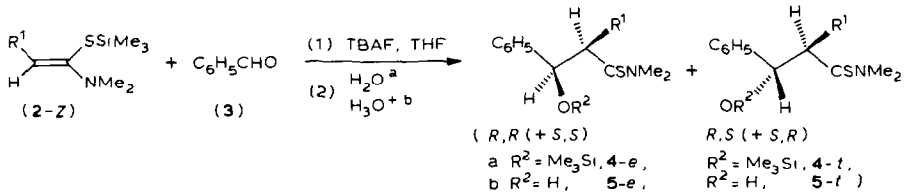
The data for Scheme 1 were collected in the Fourier transform mode using a Bruker WH-250 MHz NMR spectrometer and the Aspect 2000 data system using 32 K of data memory. The pulse angle was approximatively 30° and a delay time between pulses of 30 s was used; 30 transients were acquired for each irradiation frequency. Samples of **2** were dissolved in $CDCl_3$ (concentration $\simeq 0.2$ *M*) and were vacuum degassed several times (10^{-6} torr). Subsequently the NMR tubes were sealed.

Hence, the observed NOEs prove the *Z*-configuration for *N,N*-dimethyl-*S*-trimethylsilylketene *S,N*-acetals, **2**. This result suggest also that the lithium enethiolate **1** possesses the *Z*-configuration, provided that no isomerization takes place during silylation. There are many precedents that indicate that silylation with trimethylsilyl chloride is a kinetically controlled process [9].

Fluoride ion catalyzed reaction between *N,N*-dimethyl-*S*-silylketene *S,N*-acetals and benzaldehyde

The extremely high affinity of the fluoride anion towards the silicon atom and the potential of the fluoride-mediated generation of nucleophiles have been improved previously in the aldol reaction with enolsilyl ethers [4]. In order to test the reactivity of (*Z*)-*N,N*-dimethyl-*S*-trimethylsilylketene *S,N*-acetals, we have examined the reaction of **2**-*Z* with an equimolar amount of benzaldehyde in THF under the influence of a catalytic amount (5 mol%) of tetrabutylammonium fluoride (TBAF).

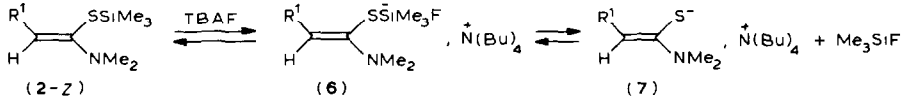
β-Siloxy- **4** or β-hydroxy-thioamides **5** are obtained in good yield even at low temperature (Scheme 2).



SCHEME 2

In sharp contrast to the corresponding lithium enethiolate, condensation of **2**-*Z* shows high *erythro*-selectivity even when R^1 is bulky (Table 1). Stereoselectivity improves with lower temperature. *Erythro*-(R^*,R^*)-β-hydroxythioamides **5**-*e*, obtained as the major products (see Table 1), were the kinetically controlled products. At low temperature (−80°C) and in 2 min, β-siloxythioamides **4**-*e* or **4**-*t*, prepared from the pure β-hydroxythioamides **5**-*e* or **5**-*t*, did not isomerize.

As previously postulated by Noyori et al. [4a,4e] and Nakamura et al. [4f] for enol silyl ethers, our results can be understood by considering the naked enethiolates of type **7** that are not interacting with any metal counter ion:



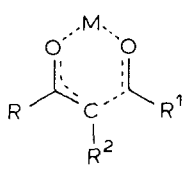
Then, in contrast to Lewis acid-complexed enolates, which are considered to react with aldehydes by a pericyclic process via the metal-linked six-membered ring transition state of type 8 [1], the observed stereoselection with *N*,*N*-dimethyl-*S*-trimethylsilylketene *S*,*N*-acetals, **2**-*Z*, is best accounted for in terms of the acyclic extended transition state of type **9** in which electrostatic repulsions are minimized [4e,4f and refs. cited therein]. In the case of the reaction with **7**, the transition state

TABLE 1

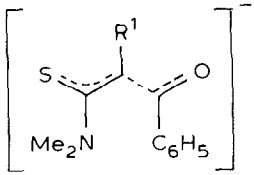
DIASTEREOSELECTIVE β-HYDROXYTHIOAMIDE FORMATION CATALYZED BY FLUORIDE ION

Entry	R^1	Reaction conditions		Yield of **5** (%)	Ratio **5**-*e*/**5**-*t* [a,b]
		T (°C)	Time (min)		
1	CH_3	−80	2	83	96/04
2	CH_3	−70	30	90	94/06
3	CH_3	−30	120	90	90/10
4	CH_3	−40	720	90	91/09
5	CH_3	−10	2	86	84/16
6	$(CH_3)_2CH$	−80	2	55	81/19
7	$(CH_3)_2CH$	−30	60	60	74/26

[a] Determined on the crude reaction product by ^1H NMR spectroscopy (250 MHz) or/and HPLC (Silica gel Si-60, 25 cm, 5 μ, petroleum ether-CH_2Cl_2 gradient). [b] *Erythro*-(R^*,R^*) or *threo*-(R^*,S^*) configurations established previously [2,3], except for **5**-*e*, $R^1 = CH(CH_3)_2$: see experimental section.

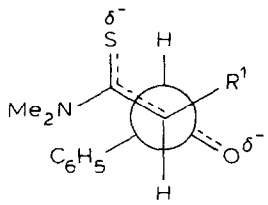


(8)



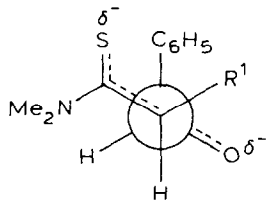
(9)

10, leading to the *erythro* adduct, is sterically favored over the diastereomeric *threo* transition state **11**, because the latter suffers repulsive *gauche* R^1/C_6H_5 interaction.



+ enantiomer

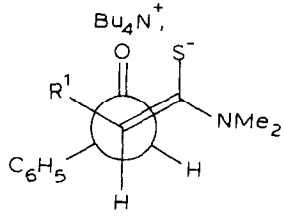
(10)



+ enantiomer

(11)

We cannot exclude, for the *erythro*-selective formation of **4** or **5**, a transition state **12**, following the topological rules proposed by Seebach et al. [10] for joining two dimensionally chiral stereogenic centers.



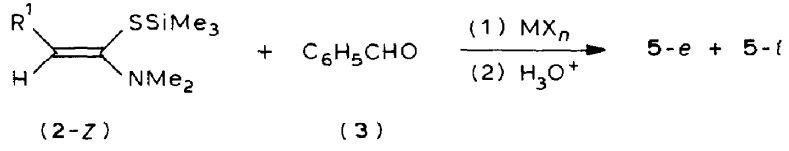
(12)

Reaction of *N,N*-dimethyl-*S*-trimethylsilylketene *S,N*-acetals with benzaldehyde activated by Lewis acid

It is difficult to cover all cases of the application of the reaction of silyl enol ethers with electrophiles activated with Lewis acids. The area has been well reviewed [11] and Mukaiyama et al. [12,13] have shown it is possible to promote regiospecific and chemiospecific cross-aldol reactions under mild conditions of a range of silyl enol ethers and aldehydes or ketones, activated with stoichiometric amounts of titanium(IV) chloride. The aldol product can also be obtained with other Lewis acid activators: ZnX_2, $BF_3 \cdot OEt_2$, $SnCl_4$, $AlCl_3$, etc [11]. It has also been shown that in the case of aldehydes or ketones sensitive towards $TiCl_4$, the desired addition product can be obtained by using $TiCl_4$-$Ti(OPr\text{-}i)_4$ together [14]. The stereochemistry of Lewis acid-mediated aldol reactions has not been systematically studied and in the extraordinary amount of results published during the last 5 years, the striking difference in the stereoselectivity of enol silanes and the corresponding lithium

enolates [15] has not yet been fully elucidated and the mechanistic aspects are currently unclear, in particular with respect to the Lewis acid.

We report here our study of the condensation of **2-Z** with benzaldehyde activated by several Lewis acids (Scheme 3) (Tables 2 and 3).



SCHEME 3

TABLE 2

REACTION OF **2-Z** WITH BENZALDEHYDE IN THE PRESENCE OF VARIOUS METAL SALTS

Entry	R^1	MX_n [a]	Reaction conditions		Yield of **5** (%)	Ratio [b] **5-e/5-t**
			T (°C)	Time (h)		
8	CH_3	$TiCl_4$	−78	1/2	80	24/76
9	CH_3	$TiCl_4$	−78	1/60	83	25/75
10	CH_3	$TiCl_4 + Ti(OPr\text{-}i)_4$ [c]	−35	1	90	16/84
11	CH_3	$TiCl_4 + Ti(OPr\text{-}i)_4$	−85	1/60	75	13/87
12	CH_3	$TiCl(OPr\text{-}i)_3$ [d]	−80	5/60	64	29/71
13	CH_3	$BF_3 \cdot OEt_2$	−70	1/2	80	40/60
14	CH_3	$SnCl_4$	20	1/2	70	30/70
15	$CH(CH_3)_2$	$TiCl_4$	−80	2/60	60	45/55
16	$CH(CH_3)_2$	$TiCl_4 + Ti(OPr\text{-}i)_4$	−80	5/60	40	61/39
17	$CH(CH_3)_2$	$TiCl_4 + Ti(OPr\text{-}i)_4$	−45	1	60	60/40

[a] Ratio MX_n/**2-Z** = 1; solvent CH_2Cl_2. [b] Determined on the crude reaction product by ^{1}H-NMR spectroscopy (250 MHz) or/and HPLC (silica gel Si-60, 25 cm. 5 μ, petroleum ether-CH_2Cl_2 gradient). [c] The mixture forms a mixed ligand titanium compound $TiCl_2(OPr\text{-}i)_2$ by disproportionation [16]. [d] Prepared according to refs. 16 and 17.

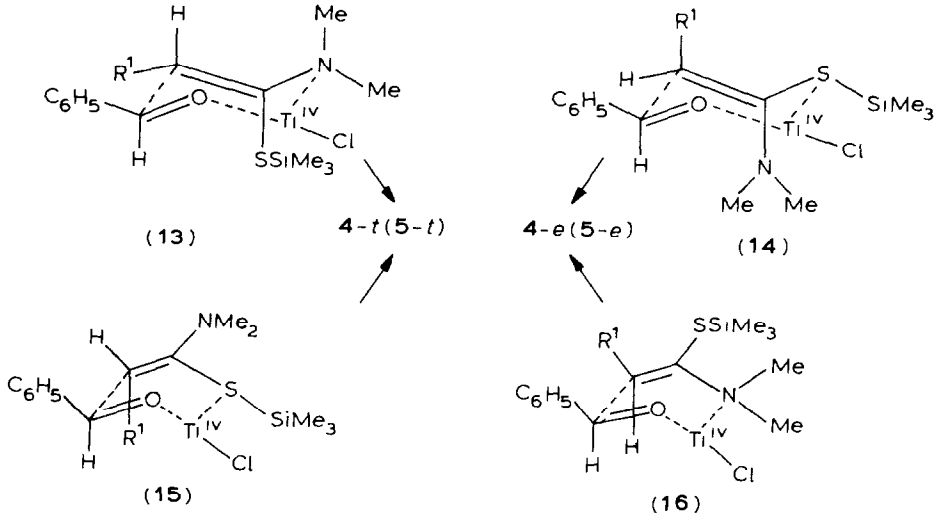
TABLE 3

REACTION OF **2-Z** WITH BENZALDEHYDE IN THE PRESENCE OF $ZnBr_2$. EFFECT OF THE AMOUNT OF SALT AND SOLVENT

Entry	R^1	Ratio $\frac{ZnBr_2\ (mol)}{2\text{-}Z\ (mol)}$	Solvent	Reaction conditions		Yield of **5** (%)	Ratio **5-e/5-t**
				T (°C)	Time (h)		
18	CH_3	0	THF	20	12	0 [a]	–
19	CH_3	0.022	THF	−15	12	90	45/55
20	CH_3	0.20	THF	−15	12	90	55/45
21	CH_3	1	THF	−15	12	90	72/28
22	CH_3	1	THF	−20	5/60	88	76/24
23	$CH(CH_3)_2$	1	THF	−20	5/60	25	30/70
24	CH_3	0.022	CH_2Cl_2	−15	12	75	10/90
25	CH_3	0.05	CH_2Cl_2	−15	12	70	20/80
26	CH_3	1	CH_2Cl_2	−15	12	85	58/42
27	CH_3	1	CH_2Cl_2	20	12	85	57/43

[a] Thioamide and benzaldehyde are entirely recovered.

Tables 2 and 3 show that of the several Lewis acids, TiX_4 and catalytic amounts of $ZnBr_2$ in CH_2Cl_2 are the best ones to provide *threo*-β-hydroxythioamides **5**-*t* with $R^1 = CH_3$, in spite of the *Z*-configuration of *N*,*N*-dimethyl-*S*-silylketene *S*,*N*-acetals **2**. While the exact mechanism of the titanium tetrachloride-promoted cross-aldol condensation is not known [12,18], several authors [19,20] have ruled out the possibility of a titanium enolate as an intermediate in this reaction. To corroborate this hypothesis we have prepared titanium enethiolate from lithium enethiolate according to the method described for titanium enolate [18,21]. The titanium enethiolate $R^1CH{=}C[STi(OPr\text{-}i)_3]NMe_2$ affords poor *erythro*-stereoselectivity in reaction with benzaldehyde ($R^1 = CH_3$; 15 min, −85°C, ratio **5**-*e*/**5**-*t* = 40/60). It seems difficult to visualize the stereoselection of the reaction (Table 2) occurs only by transition states with chair- or boat-like structures **13**–**16** (Scheme 4) usually proposed for cross-aldol reactions.



SCHEME 4

A stronger S–titanium bond, because of a weakened S–silyl bond, and minimized R^1/C_6H_5 interaction are in favor of **15**, but the lack of stereoselectivity when R^1 becomes bulkier is difficult to rationalize. When the steric hindrance of R^1 increases *, the reaction could involve more or less an acyclic transition state as considered earlier in this paper.

It has previously been postulated that in the Lewis acid complex the aldehydo-oxygen is *syn* to the hydrogen [22–24]. But ^1H and ^{13}C NMR studies, actually in progress, are aimed at showing that the aggregation of TiX_4 with aldehydes depends on ligand variations. This aggregation around the titanium atom would play an important role in controlling the stereochemical course in the addition step. The influence of the nature of the ligands at titanium on chemioselectivity and diastereoselectivity has already been observed [18,25]. The same problem of aggrega-

* When $R^1 = CH(CH_3)_2$ high *threo*-selectivity can be obtained by condensation with lithium enethiolate (**5**-*t*/**5**-*e* = 95/5) [2].

tion around the Zn atom would occur in accounting for the differences of stereoselectivity reported in Table 3. It would then be hazardous to postulate a single transition state type in this case.

Conclusion

N,N-Dimethyl-*S*-trimethylsilylketene *S,N*-acetals **2**, which are shown to have a *Z*-configuration afford under suitable conditions either *erythro*- or *threo*-β-hydroxythioamides with high selectivity.

Erythro aldol derivatives are obtained by fluoride-catalyzed addition of **2** to benzaldehyde whatever the R^1 substituent on **2**. *Threo* aldol derivatives can be formed with TiX_4- or catalytic $ZnBr_2$-mediated aldehyde condensations, if R^1 is not too bulky. NMR investigations of aldehyde-TiX_4 complexes suggest that mechanistic details might be much more complicated than those usually postulated from simple monomeric formula. Further investigations will be necessary to elucidate the mechanisms of these reactions.

Experimental

(Z)-N,N-Dimethyl-S-trimethylsilylketene S,N-acetals 2

These were prepared according to a literature procedure [26] from the lithium enethiolates **1**, generated from the corresponding thioamides [2].

TBAF-catalyzed aldol-type condensation

To a stirred solution of TBAF (10^{-3} mol in 1 ml of THF) dried over molecular sieves, is added a mixture of benzaldehyde (0.02 mol) and **2**-*Z* (0.02 mol) under an N_2 atmosphere, at the temperature indicated in Table 1. The resulting mixture is stirred for a few min, quenched at −80°C by the addition of water, and warmed to room temperature. Desilylation is achieved with 1 *M* HCl or with 40% HF and **5** is extracted with ether. The organic extracts are combined, dried and concentrated in vacuo. Ratios **5**-*e*/**5**-*t* are determined on the crude oil. The purification of the oil is achieved by HPLC [2]. It has been verified that no isomerization occurs during the desilylation of **4**.

Lewis-acid catalyzed formation of 5

(a) Materials. Methylene chloride is dried on alumina just before use and distilled over magnesium. $TiCl_4$ and $Ti(OPr\text{-}i)_4$ are distilled and stored under argon. $ZnBr_2$ is prepared from Zn and dibromoethane in THF and desolvated. THF is distilled over sodium/benzophenone.

(b) Aldol reaction. To a stirred solution of benzaldehyde (0.02 mol) in dry methylene chloride (10 ml), cooled at −40°C, is added MX_n (0.02 mol or in the ratio indicated in Table 3). The mixture is stirred for 15 min under a N_2 atmosphere and then cooled to the temperature indicated in Tables 2 and 3. A methylene chloride (10 ml) solution of **2**-*Z* (0.02 mol) is added dropwise to the solution and stirred for a few min (or the time indicated in Tables 2 and 3). After quenching with water at −80°C, desilylation is achieved and subsequent extractive workup with methylene chloride provides crude **5**.

Spectra and structures

(a) IR and ^{1}H NMR spectra of **5**-*e* and **5**-*t* have been reported [2] except those for $C_6H_5CH(\alpha)(OH)CH(\beta)(CH(CH_3)_2)CSNMe_2$ (R^*,R^*)**5**-*e*; ^{1}H NMR ($CDCl_3$): δ_{TMS} 5.02 (H(α) d, $J(\alpha,\beta) = 2.6$ Hz), 3.31 (H(β), dd), 3.47 and 3.38 ($N(CH_3)_2$, s). IR (KBr) ν(OH): 3256 cm^{-1}.

(b) The structure of **5**-*e* ($R^1 = CH(CH_3)_2$) is determined by transforming the diastereoisomer to the corresponding amino alcohol, $C_6H_5CH(\alpha)(OH)CH(\beta)$-$(CH(CH_3)_2)CH_2NMe_2$, **17**, with $LiAlH_4$ reduction [2]. Reduction of $C_6H_5CH(\alpha)(OH)CH(\beta)(CH(CH_3)_2)CONMe_2$ *erythro* ($J(\alpha,\beta) = 6.3$ Hz) afford the same amino-alcohol, **17** ($J(\alpha,\beta) = 3$ Hz). The stereochemistry of β-hydroxyamide has been established previously [27].

The IR spectra were recorded on a Perkin–Elmer 257 spectrometer and the ^{1}H NMR spectra were obtained on a Bruker 250 MHz spectrometer.

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