

REGIOSELECTIVITY OF S-SILYLKETENE S,N ACETALS
AND TITANIUM - (ATE) - ENETHIOLATES ADDITION
TO UNSATURATED KETONES

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Summary : (Z) S-Silylketene S,N acetals react with α -enones to afford exclusive 1-2 addition. Titanium enethiolates and titanium - ate - complexe enethiolates undergo 1-2, 1-4 addition.

In a previous paper¹ we established that lithium enethiolates 1 generated from N-dimethylthioamides $R^1CH_2CSN(Me)_2$ provide either 1-2 or 1-4 addition with α -enones $C_6H_5-CH=CH-CO-R^2$. The regioselectivity of the addition was determined by R^1 and R^2 . Recently we reported that condensation of (Z) S-silylketene S,N acetals 2 in the presence of TBAF or Lewis acids catalysis affords β -hydroxythioamides in good yields². Diastereoselectivities of the aldol condensations via lithium enethiolates 1 or via S-silylketene S,N acetals 2 were quite different. In this communication, we wish to report regioselective 1-2 addition of 2 to α -enones whatever R^1 and R^2 . Regioselectivity of the addition of titanium enethiolates 5 and titanium - ate - complexes 6 has been also studied.

I - Reaction of S-silylketene S,N acetals 2 with α -enones in the presence of chlorotitanium triisopropoxide.

The area of applications of reaction of silyl enol ethers and silyl ketene acetals with electrophiles activated with Lewis acids has been well reviewed³. Mukaiyama and co-workers have reported that silyl enol ethers⁴ and O-silyl ketene acetals⁵ undergo Lewis-acid catalyzed 1-4 addition to α - β unsaturated compounds and their derived acetals. In sharp contrast with those authors, condensation of (Z) S-silylketene S,N acetals 2 with α -enones activated by $ClTi(OiPr)_3$ affords exclusively 1-2 addition in good yields whatever R^1 and R^2 (table I).

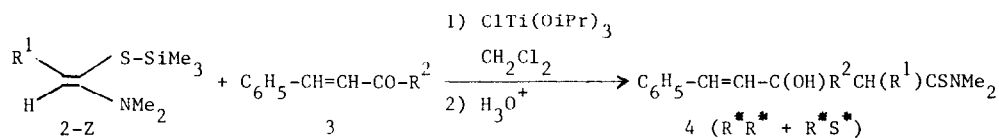


Table I : Regioselective 1-2 addition of $\underline{2-Z}$ with α -enones in the presence of ClTi(OiPr)_3 *.

Entry	R ¹	R ²	Reaction conditions		Yield $\underline{4}$ ($\underline{4a}/\underline{4b}$) **	
			Temp(°C)	Time (hr)	%	
1	CH ₃	CH ₃	-40	1	82	(65/35)
2	CH ₃	C ₆ H ₅	0	1	84	(48/52)
3	(CH ₃) ₂ CH	CH ₃	0	1	47	(30/70)
4	(CH ₃) ₂ CH	C ₆ H ₅	-45	1	48	(47/53)
5	(CH ₃) ₂ CH	C ₆ H ₅	0	1	64	(47/53)
6	(CH ₃) ₂ CH	C ₆ H ₅	20	2	67	(50/50)

* ClTi(OiPr)_3 was prepared according ref. 6 .

** Hydroxythioamides $\underline{4}$ were obtained as diastereoisomeric mixtures.

Diastereoisomeric ratio $\underline{4a}/\underline{4b}$ determined by ¹H-NMR (250 MHz)⁷ and HPLC (Silica gel Si-60, 25 cm, 5 μ , CH₂Cl₂ - petroleum ether gradient).

$\underline{4a}$ is assigned in all cases to the isomer with higher R_F and $\underline{4b}$ to that with a lower R_F value.

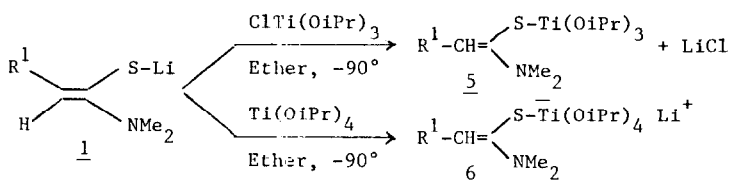
We wish to report also that condensation of (Z) O-silylketene O,N acetal $\text{CH}_3\text{-CH=C} \begin{array}{l} \text{OSiMe}_3 \\ \text{NMe}_2 \end{array}$ with benzilidene acetophenone (R² = C₆H₅) affords a mixture of 1-2/1-4 addition (20/80, reaction conditions identical to entry 2).

The striking difference in regioselectivity of silylketene acetals, O-silylketene O,N acetals, S-silylketene S,N acetals (and lithium enethiolates) promises to be useful in synthetic organic chemistry.

II - Reaction of titanium-enethiolates $\underline{5}$ and titanium-ate complexes $\underline{6}$ with α -enones.

Despite extensive research about the enolate anion, present knowledge relating to the condensation of transition metal enolates with α -enones is limited^{8,9}.

We have prepared titanium enethiolates $\underline{5}$ and titanium-ate complexes $\underline{6}$ according methods described for titanium-(ate) enolates^{10,11}.



Reetz⁸ and Seebach⁹ have shown that by mixing solutions of R-Li and Ti(OiPr)₄, a reagent is formed which behaves neither as R-Li nor, however as R-Ti(OiPr)₃. Condensation of 5 and 6 with α-enones confirms this difference (table II).

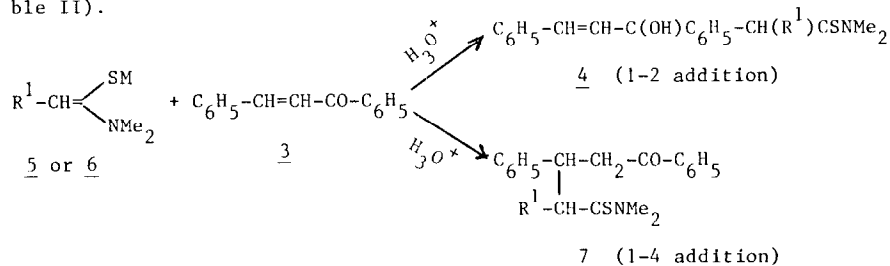


Table II : Addition of 5 or 6 with benzylidene acetophenone.

Entry	R ¹	M	Reaction conditions		Ratio			Yield % (4+7)
			Temp(°C)	Time (hr)	<u>4/7</u>	<u>4a/4b</u>	<u>7a/7b</u>	
7	CH ₃	Ti(OiPr) ₃	-80	0,5	100/ ^{**}	50/50	-	80
8 [*]	CH ₃	Ti(OiPr) ₃	-40	1	100/ ^{**}	100/-	-	50
9 [*]	CH ₃	Ti(OiPr) ₄ Li ⁺	-50	1	45/55	38/62	35/65	95
10	(CH ₃) ₂ CH	Ti(OiPr) ₃	-80	0,5	-	-	-	0
11	(CH ₃) ₂ CH	Ti(OiPr) ₄ Li ⁺	-80	0,5	^{**} /100	-	^{***}	25
12 [*]	(CH ₃) ₂ CH	Ti(OiPr) ₄ Li ⁺	-50	1	^{**} /100	-	^{***}	80

* α-enone is added at -80°C to a solution of 5 or 6 and after 5 mn, the mixture is allowed to warm up at temperature indicated in table II.

** No trace of isomer 7 (or 4) disclosed by NMR and HPLC.

*** Only one diastereoisomer 7 disclosed by NMR and HPLC and identical to lithium enethiolate synthesis¹.

Kinetic control for entry 7-9-11 were verified as follows : an independently synthesized 4a/4b mixture (20/80) from α-enone and S-silylketene S,N acetals was reacted with CH₃Ti(OiPr)₃ or with CH₃Ti(OiPr)₄Li⁺ liberating CH₄ and the Ti(ate)-enethiolates. The usual work up affords unchanged 4a/4b mixture (20/80).

In case of α-β unsaturated carbonyl compounds, methyl titanium triisopropoxide¹² and titanium-ester enolate⁸ add in a 1-2 manner. Selectivities in tables I and II are presently difficult to rationalize, but reactivities and selectivities differences corroborate hypothesis that TiX₄ promoted cross-aldol condensation with S-silylketene S,N acetals 2 does not involve titanium enethiolate as intermediate¹³. We are working on further experiments aimed at elucidate mechanistic aspects of those additions.

References and notes

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7. IR and $^1\text{H-NMR}$ Spectra of 4a and 4b have been reported¹ except for
 $\text{C}_6\text{H}_5\text{-CH}_\alpha\text{=CH}_\beta\text{-C(OH)C}_6\text{H}_5\text{CH}_\delta(\text{CH}(\text{CH}_3)_2)\text{CSNMe}_2$: δ_{TMS} ppm, CDCl_3 ; 4a : 6.5, 6.20 ($\text{H}_\alpha, \text{H}_\beta$, d,d, $J_{\text{H}_\alpha\text{H}_\beta} = 15.6$ Hz) ; 3.67 (H_δ , d) ; 3.56 and 3.43 ($\text{N}(\text{CH}_3)_2$, s) ; 0.88 and 0.51 (CH_3 , d). 4b : 6.82, 6.48 ($\text{H}_\alpha, \text{H}_\beta$, d,d, $J_{\text{H}_\alpha\text{H}_\beta} = 15.7$ Hz) ; 3.60 (H_δ , d) ; 3.06 and 3.24 ($\text{N}(\text{CH}_3)_2$, s) ; 1.17 and 1.00 (CH_3 , d).
 In this case ($\text{R}^1 = (\text{CH}_3)_2\text{CH}$, $\text{R}^2 = \text{C}_6\text{H}_5$) lithium enethiolate synthesis affords exclusively 1-4 addition whatever condition reactions¹.
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