A convenient diastereoselective synthesis of β -aminodithioesters from mono-S-trimethylsilyl ketene dithioacetals.

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Abstract : In the presence of Lewis acid catalysts, mono-S-trimethylsilyl ketene dithioacetals reacted with imines to afford the corresponding β -aminodithioester in acceptable to good yields with anti relative selectivity.

Little is known about β -aminodithioesters.¹⁻⁴ Nevertheless they may be considered as useful precursors of potent β -thiolactams. Their synthesis from 1-methylthioethenethioate (available by deprotonation of the corresponding dithioester in a solution of LDA) with different imines failed with the exception of N-p-tolylsulfonylimine(see scheme 1).



scheme 1

We now disclose our successful diastereoselective synthesis of various β -aminodithioesters from mono-S-trimethylsilyl ketene dithioacetals and imines.

(Z) mono-S-trimethylsilyl ketene dithioacetals are easily available by classic routes⁵⁻⁶ or by our recently reported method based on the reaction of dithioesters with trimethylsilyl iodide formed *in situ* in the presence of triethylamine(see scheme 2).⁷





They were reacted with imines under Lewis acid catalysis.

For optimising both yield and diastereoselectivity, this reaction was performed with various catalysts and standard partners : N-benzylideneaniline and S-trimethylsilyl ketene dithioacetals derived from methyldithiopropanoate(see scheme 3 and Table I).



scheme 3

Entry	Catalyst	Solvent	T° C	Time	Syn/Anti ^(a)	Yield	
	-			(h)	Ratio	(%)	
1	ZnCl ₂	THF	RT	3	15/85	72	
2	ISiMe ₃	CH ₂ Cl ₂	-78 to RT	3	22/78	70	
3	TMSTf	CH ₂ Cl ₂	RT	3	-	-	
4	NaI	CH₃CN	RT	3	-	-	
5	I ₂	THF	RT	3	-	-	
6	ZnI2	THF	RT	3	35/65	80	
7	TrSbCl ₆	CH ₂ Cl ₂	RT	3	12/88	40	
8	ZnI ₂ /Et ₃ N	THF	RT	3	08/92	50	

(a) determined by H.P.L.C. analysis (silica gel, 25 cm, 5µ) with ethyl acetate and n-heptane as eluant.

Two diastereoisomeric β -aminodithioesters were formed with quite high diastereoselectivity(except in entry 6) and acceptable to good yields.

The predominant diastereoisomer was always the second eluted in HPLC analysis and there was no inversion of selectivity with ISiMe₃ as has been observed with the oxygenated analogue.⁸ Nevertheless, a comparison with Mukaiyamas results seems hazardous. Indeed the ketene silyl acetal used had the E geometry, contrary to our silyl ketene dithioacetals. Catalysts such as TMSTf,⁹ NaI and I₂ were entirely useless. Addition of triethylamine to ZnI₂ enhanced the selectivity with a loss of yield from 35/65 to 08/92(see entries 6 and 8), probably by epimerisation toward the more stable diastereoisomer.

Geometry assignment of the two diastereoisomeric β -aminodithioesters was easily done after the transformation of a mixture of the two dithioesters into their corresponding esters and comparison with known β -aminoesters.¹⁰⁻¹¹ Thus the reaction of the mixture of syn and anti β -aminodithioesters 1.5/98.5(obtained by an overnight reaction between a mixture of β aminodithioesters and triethylamine) with mercuric trifluoroacetate in the presence of methanol,¹²⁻¹³ yielded without epimerisation a mixture of major anti and syn β -aminoesters in the same ratio(see scheme 4).

The stereochemistry of the major product was established on the basis of vicinal coupling constant J $\alpha\beta$ anti-J $\alpha\beta$ syn.¹⁰⁻¹¹





Scope and limitation of this reaction was futhermore stated by conducting the same condensation with various imines in the presence of either $ZnCl_2$ or ZnI_2 , the two more suitable catalysts(see scheme 5 and Table II).



scheme 5

Entry	R ¹	R ²	Catalyst	Yield (%)	Syn/Anti Ratio ^(a)
1	Ph	Ph	ZnCl ₂	72	15/85
			ZnI ₂	80	35/65
2	Ph	CH ₂ Ph	$ZnCl_2$	-	-
			ZnI2	-	-
3	Ph	Me	ZnCl ₂	-	-
			ZnI ₂	-	-
4	Ph	CO ₂ Me	ZnCl ₂	70	27/73
			ZnI2	77	27/73
5	Ph	SO2Ph	ZnCl ₂	-	-
			ZnI ₂	-	-
6	Thienyl	Ph	ZnCl ₂	40	06/94
			ZnI2	60	10/90
7	PhCH=CH	Ph	ZnCl ₂	-	-
			ZnI2	-	-
8	Ph	PhOMe	ZnCl ₂	-	-
			Znla	-	-

Table II

(a) determined by H.P.L.C. analysis (silica gel, 25 cm, 5µ) with ethyl acetate and n-heptane as eluant.

As shown in Table II, ZnCl₂ gave better diastereoselectivity, as high as 06/94(entry 6) at the expense of yield. Imines derived from methylamine, benzylamine, phenylsulfonylamine and cinnamylideneaniline afforded neither the expected β -aminodithioester nor a possible β -thiolactam resulting from a hypothetic intraaminolysis reaction.

The reactivity of these new compounds has yet to be explored and works are in progress namely the internal cyclisation of these β -aminodithioesters into the corresponding β -'thiolactam, the aldol reaction and thioClaisen rearrangement of the corresponding ketene dithoiacetal.

A typical procedure was described for this reaction : to a solution of imine(1,7 mmole ; 300 mg) and dithioacetal(2 mmole ; 384 mg) in dichoromethane(5 ml) stirred at room temperature, $ZnI_2(1,7 \text{ mmole}; 530 \text{ mg})$ in dichloromethane(5 ml) was added. After stirring 2h at room temperature under N₂ atmosphere, the reaction mixture was quenched with an aqueous solution of ammonium choride. The organic materials were extracted with dichloromethane and the combined extracts were dried over MgSO₄. After concentration under reduced pressure, the residual material crystals were washed with petroleum ether on a glass filter to give (368 mg; 72%) of β-aminodithioester with sufficient purity(characterisation by IR, NMR, Mass spectrum and microanalysis).

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