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STEREOSPECIFIC MICHAEL ADDITION OF DITHIOESTER ENETHIOLATES WITH ACYCLIC ENONES

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Abstract - Cis lithium enethiolates, generated from substituted dithioesters, undergo 1,4-addition with various β-monosubstituted α-unsaturated ketones. With acyclic enones one of the two resulting diastereomeric 5-oxodithioesters is predominantly formed (ratio up to 95 : 5). Its anti configuration was proven by chemical correlation in one case. Evidence for the stereospecificity of this Michael addition is given.

Recent reports [1-4] on the diastereoselectivity of the Michael addition of enolates prompt us to disclose that the reaction of enethiolates with non-biased acyclic enones is stereospecific and permits diastereocontrol.

So far the stereochemistry of the conjugate addition of prochiral enolates, and equivalents, has been examined in detail with three types of prochiral acceptors : nitro alkenes, [5-10] α-unsaturated esters [1,11-13] and ketones. [2-4, 14-16] However the utilization of α-ethylenic ketones is restricted by i) competing reactions, e.g. kinetic 1,2-addition, cyclocondensation of 1,4-adducts, ii) the need of either a phenyl or a tert-butyl group. We wish to report a solution to these limitations.

The present study starts from our previous observations that i) lithium enethiolates are soft nucleophiles which undergo regio selective 1,4-addition with a variety of α-unsaturated ketones, [17-22] ii) kinetic deprotonation of thiocarbonyl compounds preferantially afford cis enethiolates, [19,23-27] in contrast to the trans geometry of enolates obtained from most carbonyl compounds.

We first surveyed the behaviour of various enones with a 3 : 1 cis/trans enethiolate mixture generated from methyl dithiopropanoate 1 . [23-24] After reaction at low temperature, 5-oxodithioesters 2-6 are obtained (table 1). The diastereoisomers, which are easily discernable by ^1H and ^{13}C NMR, could be separated by medium pressure liquid chromatography. [28] The stereochemical data fall into two categories. With cyclic enones, a poor diastereoselection was observed. With acyclic enones, the 3 : 1 diastereomeric ratio is the

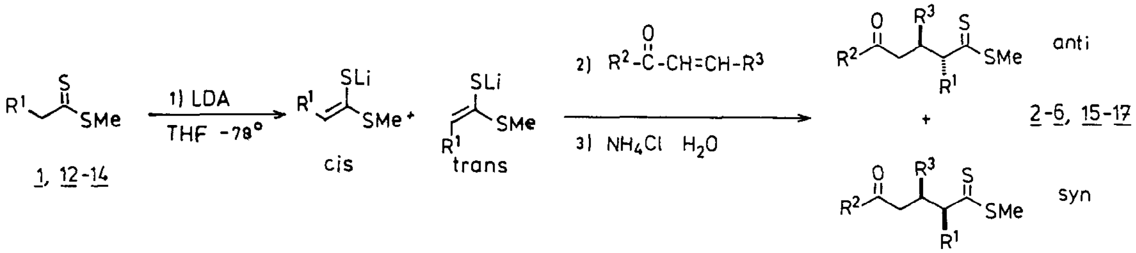
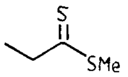


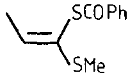
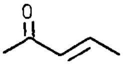
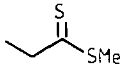
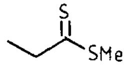
Table 1.

Dithio-ester	Thioenolates ratio	Enone	Addition conditions temp. °C	time min.	Product[28]	Diastereoisomeric ratio	Chemical yield %
 1	76 : 24	2-Cyclopentenone	-40	10	2	61 : 39	67
		2-Cyclohexenone	-40	20	3	51 : 49	70
		2-Cycloheptenone	-40	20	4	50 : 50	82
		3-Penten-2-one	-50	10	5	75 : 25	66
		Chalcone	-70	10	6	72 : 28	69

same as that of the isomeric enethiolates.

To gain further evidence for stereospecificity in the acyclic series, we submitted the same enethiolates, but of varied cis/trans composition, to the 1,4-addition with 3-penten-2-one at -50°C (table 2).

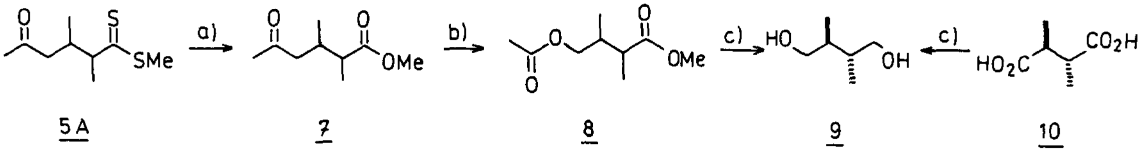
Table 2.

Generation of enethiolates			Diastereoisomers	Chemical
reactants	*cis* / *trans* ratio	Enone	5 ratio *anti* / *syn*	yield %
 + MeLi	96 : 4		92 : 8	59
 + LDA	76 : 24	''	75 : 25	66
 + LHMDS	58 : 42	''	57 : 43	85

The isomer ratios of enethiolates and products 5 are almost identical. This demonstrates that the *cis* dithioester enethiolate exhibits high diastereofacial selectivity in the 1,4-addition with acyclic E enones. Preparation of a pure *cis* enethiolate leads to the adduct 5 with a stereochemical purity above 90 %.

These reactions are probably under kinetic control. Evidence for equilibration of the reaction mixture was observed only in the case of chalcone : bringing the solution to +20°C reverses the diastereoisomeric ratio (39 : 61).

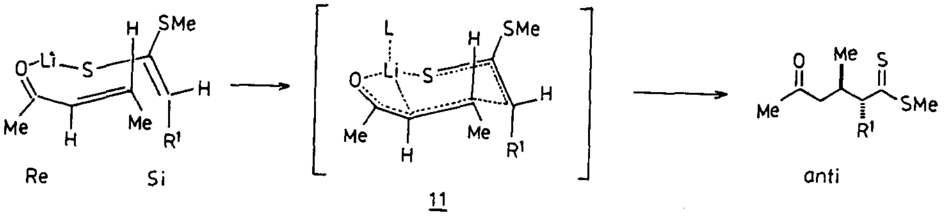
The configuration of the major diastereoisomer 5 A was assigned by transformation into 2,3-dimethylbutane-1,4-diol 9 :



a) $Hg(OCOCF_3)_2$, MeOH. b) CF_3CO_3H, CH_2Cl_2 . c) $LiAlH_4$, Et_2O.

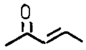
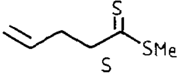
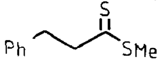
Diol 9 was identical (^{13}C NMR)[29] to the material obtained by reduction of the commercial *meso* 2,3-dimethylsuccinic acid 10. The major 5-oxodithioester 5 A has thus the *anti* configuration.

To interpret this stereochemistry we assume a Re-Si facial attack of the enone on the enethiolate, leading to a pseudo-cyclic transition state 11 in which i) the lithium atom is coordinated to sulfur, oxygen and to carbon-3 (as for 3,4-additions), ii) the methyl and acetyl groups of the E enone occupy equatorial positions.



This rationalisation could also explain the poor selectivity observed with cyclic enones. Their Z geometry sets the above substituents in the equatorial and axial positions and thus decreases the energy difference between 11 and the isomeric transition state resulting from Re-Re attack. Furthermore cyclic enones have a fixed s-trans configuration.

We also examined various 2-substituted dithioesters 12-14. Kinetic deprotonation with LDA furnishes the corresponding enethiolates that were added to 3-penten-2-one. The diastereoisomeric ratio of the isolated[28] 5-oxodithioesters 15-17 is superior or equal to 4 : 1 and still similar to the enethiolates ratio.

Dithioester		Thioenolates ratio[30]	Enone	Addition conditions °C	min.	Product[28]	Diastereoisomeric ratio[31]	Chemical yield %
nHexCS_2Me	12	85 : 15		-10	15	15	86 : 14	76
	13	95 : 5	"	-5	30	16	95 : 5	61
	14	n.a.	"	-30	30	17	80 : 20	57

A highly diastereoselective addition was obtained from methyl 4-pentenedithioate 13, as a consequence of its selective deprotonation.[32]

Our study confirms the feasibility of kinetic diastereoselective Michael reaction of enolate type intermediates, as was recently reported for a variety of acceptors.[1,2,4-8,11,12,14,16] We have now added the case of acyclic enones, without having recourse to phenyl or tert-butyl groups.[2-4,14-16] We have demonstrated the stereospecificity of the reaction. The versatility of the dithioester group[20,34] of the products 5, 6, 15-17 should offer useful developments of this addition for organic synthesis. This new means of diastereocontrolled creation of two vicinal asymmetric centers by carbon-carbon bond formation in the acyclic series[35] complements the Ireland version[36] of the Claisen rearrangement.[37]

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30 Data obtained by the technique previously reported.[23,24]
31 The relative composition of diastereoisomeric mixtures was estimated from ^{1}H 60 MHz NMR (350 MHz for compound 16) signals of the acetyl group and confirmed by ^{13}C NMR or HPLC (heptane/ethyl acetate elution on 10 microns SiO$_2$ column).
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