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Completely Regioselective Reversals for an Addition Reaction of Ambident Sulphur Nucleophiles to Michael Acceptors

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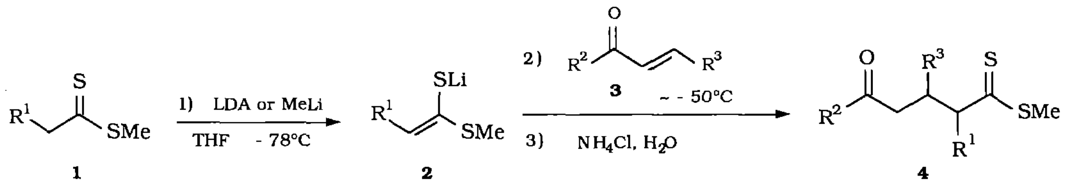
Abstract. - Reaction of titanium enethiolates with α-unsaturated ketones leads selectively to 3-hydroxy 4-unsaturated alkanedithioates, arising from a 1,2-carbon-addition, whereas aluminium enethiolates give oxoketene dithioacetals, from exclusive 1,4-sulphur-addition.

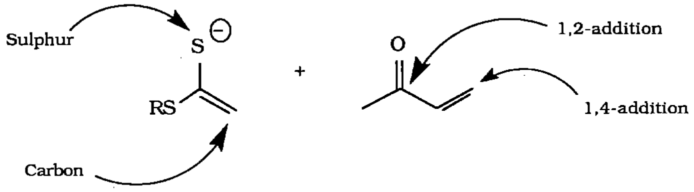
Our group has shown that enethiolates **2**, arising from deprotonation of thiocarbonyl compounds **1**, exhibit **soft** nuclophilic behaviour. Their reaction with α-unsaturated ketones leads to regioselective **1,4-additions** under kinetic control (1-7).



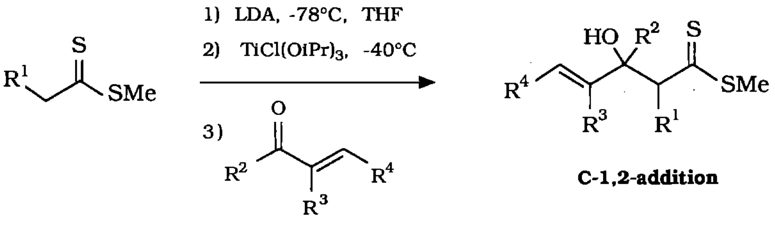
The synthetic interest of this reaction led us to investigate its scope and the influence of various factors: nature of the thiocarbonyl compound (8), of the Michael acceptor (9). We have also shown that the reaction course does not vary when replacing THF for another solvent, ether or even HMPA.

We wished to study the role of the **metallic counterpart** of the nucleophile. So far we had used **lithium**. We wondered whether this conjugate addition is specific of lithium enethiolates. Our interest was also to achieve stereocontrol by changing the metal. Having demonstrated the stereospecificity of the addition of acyclic lithium enethiolates (5), our project was to devise a stereoconvergent reaction.

During this investigation we have uncovered that the use of titanium or aluminium species leads to a complete reversal of regioselectivity, apparently without precedent in the oxygen series. Reactants are ambident: the sulphur nucleophile may react through its carbon or sulfur terminus and the acceptor may lead to 1,2- or 1,4-additions.



Lithium enethiolates were generated as usual (2, 10, 11) by proton abstraction of methyl dithioacetate **5** or propanedithioate **6** with LDA or MeLi. Metal exchange was carried out by addition of tri(isopropoxy)titanium chloride (4 equiv.) at -40°C. The resulting mixtures were treated with three enones: pent-3-en-2-one **7**, 3-methylbut-3-en-2-one **8** and cyclohex-2-enone **10**. After quenching with aqueous ammonium fluoride we obtained dithioesters **11-14** (12) bearing a 3-hydroxy moiety together with a 4-unsaturation.



5 $R^1=H$

6 $R^1=Me$

11 $R^2=R^4=Me$, $R^3=H$

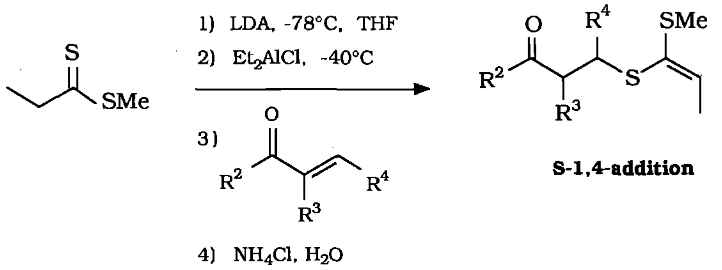
12 $R^2=R^3=Me$, $R^4=H$

13 $R^2,R^4=(CH_2)_3$, $R^3=H$

14 $R^2=R^4=Me$, $R^3=H$

Such aldols arise (11, 13-17) from **1,2-additions** from the **carbon** site of the nucleophile. This behaviour is probably related to the relatively **hard** character of the titanium nucleophiles as compared to the lithium species and to their Lewis acidity. We have thus achieved a second orientation amongst the four that are possible from two reactants which are both ambident.

Lithiated methyl propanedithioate was then treated with 3 eq. of diethylaluminium chloride at -40°C. Enones **7-10** were made to react with the resulting solution for 30 min. After quenching with water, we observed the selective formation of ketones **15-18**, bearing a ketene dithioacetal moiety (12). Their structure reveals a dramatic change of selectivity: the nucleophile affords a **1,4-addition** through its **sulphur**, instead of carbon.



6

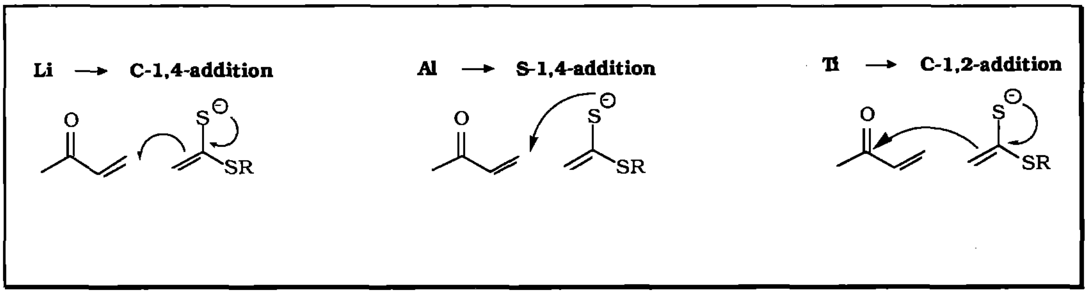
S-1,4-addition

15	$R^2=R^4=Me$, $R^3=H$
16	$R^2=R^3=Me$, $R^4=H$
17	$R^2,R^4=(CH_2)_2$, $R^3=H$
18	$R^2,R^4=(CH_2)_3$, $R^3=H$

Attack from the **sulphur** of an enethiolate is common with halides (18-20), but rare with carbonyl electrophiles (with exception of acyl halides). We had previously only observed it once (21) with a sterically hindered enethiolate, derived from methyl dithioisobutyrate: S-addition products were formed under kinetic control and equilibration lead to C- 1,4-addition compounds. With the present aluminium derivatives we have not been able to perform any equilibration.

The regiochemistry of the aluminium species remains to be explained. One should note that an excess (4 equiv.) of metal salt is crucial in both cases, either to effect complete metal exchange or to develop sufficient Lewis acidity.

In conclusion, by proper selection of the metallic part of a sulfur nucleophile, we are now able to achieve three out of the four orientations that are possible from two partners that are both ambident.



The use of titanium and aluminium nucleophiles has already been reported as a means to adjust selectivity towards carbonyl compounds (22). To our knowledge this tactics was not precedented so far to reverse the regiochemistry for the addition of enolate type reagents to Michael acceptors (23). Our results illustrate the often specific behaviour of thiocarbonyl compounds and enethiolates (24).

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(12) Yields are quantitative. Products are labile but, since they are more than 90 % pure, they can be used crude to avoid liquid chromatography. Selected spectroscopic data for new compounds:
11 - ^{1}H NMR: 1.20 (s, 3-Me); 1.64 (d, J = 6 Hz, Me-C=); 2.58 (s, SMe); 3.18 (s, Me-C=S); 3.52 (bs, OH); 5.48 (m, HC=CH). ^{13}C NMR (C_6D_6+CCl_4): 17.4; 19.7; 28.3; 62.5; 72.1; 123.2; 136.6; 235.2. IR (CCl_4): 3450 cm^{-1} (OH). **12** - ^{1}H NMR : 1.32 (s, 3-Me); 1.78 (s, Me-C=); 2.68 (s, SMe); 3.38 (s, CH_2-C=S); 3.98 (bs, OH); 5.02 (m, CH_2=C). ^{13}C NMR (C_6D_6+CCl_4): 19.5; 27.4; 30.1; 60.2; 75.0; 111.0; 148.7; 235.2. IR (CCl_4): 3440 cm^{-1} (OH). **13** - ^{1}H NMR : 2.65 (s, SMe); 3.22 (s, CH_2C=S); 3.45 (bs, OH); 5.62 (m, HC=CH). RMN ^{13}C (C_6D_6+CCl_4): 19.0; 19.8; 25.0; 35.4; 62.1; 69.4; 128.8; 131.7; 234.8. IR (CCl_4): 3450 cm^{-1} (OH). **14** - ^{1}H NMR : 1.18 (s, 3-Me *of minor diastereomer);* 1.20 (s, 3-Me *of major diastereomer*); 1.30 (d, J = 7 Hz, 2-Me *maj*); 1.35 (d, J = 7 Hz, 2-Me *min*); 1.60 (d, J = 7 Hz, Me-C= *min*); 1.75 (d, J = 7 Hz, Me-C=); 2.55 (s, MeS *min*); 2.70 (s, MeS *maj*); 3.35 (bs, OH); 5.5 (m, H-C=). ^{13}C NMR (C_6D_6): 17.6 (*min*); 17.6 (*min*); 17.7 (*maj*); 18.5; 19.1; 26.9 (*min*); 28.2 (*maj*); 62.8 (*min*); 63.1 (*maj*); 73.9; 123.2 (*min*); 124.3 (*maj*); 136.5 (*maj*); 137.5 (*min*); 245.6. IR (CCl_4): 3640 cm^{-1} (OH). **15** - ^{1}H NMR : 1.28 (d, J = 7 Hz, Me-CH); 1.90 (d, J = 7 Hz, Me-C=); 2.15 (s, Me-C=O); 2.3 (s, MeS); 6.1 (q, J = 7 Hz, H-C=). ^{13}C NMR ($CDCl_3$) : 16.4 (*E major isomer*); 16.5 (*Z minor isomer*); 16.8 (*Z*); 20.4 (*E*); 20.8 (*Z*) 30.3 (*Z*); 30.8 (*E*); 36.4 (*E*); 37.2 (*Z*); 50.0 (*E*); 50.4 (*Z*); 131.0 (*E*); 132.2 (*Z*); 206.2 (*E*); 206.4 (*Z*). IR (CCl_4): 1720 cm^{-1} (C=O). **16** - ^{1}H NMR : 1.20 (d, J = 7 Hz, 3-Me); 1.90 (d, J = 7 Hz, Me-C=); 2.15 (s, MeS); 2.25 (s, Me-C=O *of E major isomer*); 2.30 (s, Me-C=O *of Z minor isomer*); 6.10 (q, J = 7 Hz, H-C= of *Z*); 6.20 (q, J = 7 Hz, H-C= of *E*). ^{13}C NMR (C_6D_6 + CCl_4): 15.8 (*Z*); 16.0 (*E*); 16.3 (*Z*); 16.6 (*E*); 27.8; 28.0; 34.9; 46.7; 131.8 (*Z*); 132.2 (*E*); 134.2; 207.0. IR (CCl_4): 1710 cm^{-1} (C=O). **17** - ^{1}H NMR : 1.90 (d, J = 7 Hz, Me-C=S); 2.20 (s, MeS); 6.10 (q, J = 7 Hz, H-C=). ^{13}C NMR (C_6D_6): 16.3 (*Z major isomer*); 16.5 (*E minor isomer*); 28.7 (*E*); 29.1 (*Z*); 36.2; 41.6 (*E*); 42.1 (*Z*); 44.1 (*E*); 44.5 (*Z*); 96.2; 132.2 (*Z*); 136.3 (*E*); 212.7. IR (CCl_4): 1725 cm^{-1} (C=O). **18** - ^{1}H NMR : 1.88 (d, J = 7 Hz, Me-C=); 2.20 (s, MeS); 6.10 (q, J = 7 Hz, H-C=). ^{13}C NMR (C_6D_6): 16.1 (*Z major isomer*); 16.3 (*E minor isomer*); 16.4 (*Z*); 16.6 (*E*); 23.8 (*Z*); 30.9 (*E*); 31.2 (*Z*); 40.4 (*Z*); 43.5 (*E*); 44.0 (*Z*); 46.7 (*E*); 47.0 (*Z*); 132.6 (*Z*); 136.7 (*Z*); 204.3 (*Z*); 204.4 (*E*). IR (CCl_4): 1720 cm^{-1} (C=O).

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