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CIS-SELECTIVITY OF THE KINETIC DEPROTONATION OF DITHIOPROPANOATES.

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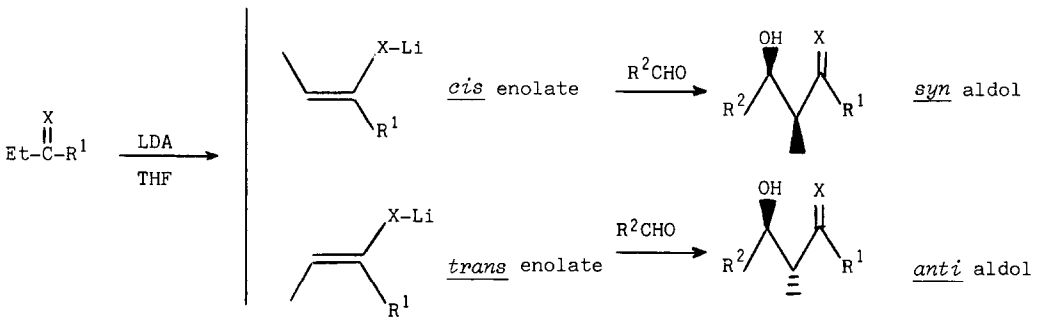
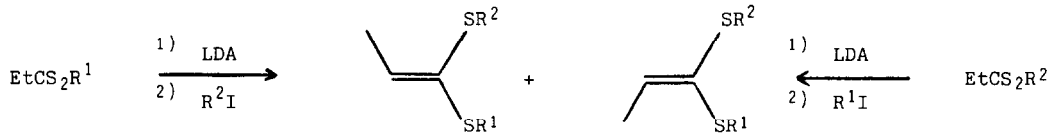
Abstract :

Deprotonation of dithiopropanoates with LDA in THF solution at -78°C afforded chiefly the cis lithium thioenolate in contrast with the trans enolization of most of carbonyl compounds. The cis geometry was proved by a thio-Claisen rearrangement.

During the past years, our group devoted a large interest to the chemistry of dithioesters [1] . Very recently we focused our attention on their thioenolates [2] . In this paper we wish to report our first results on the stereochemistry of deprotonation of dithioesters (thioenolization) with the object of performing asymetric C-C bond formation reactions α to a masked carbonyl group : aldolisation, Michaël addition, thio-Claisen rearrangement. The kinetic deprotonation of numerous carbonyl compounds has been studied :*trans* lithium enolates are formed from aldehydes [3] , esters [4,5], ketones [6], imines [7] and thiolesters [8], *cis* lithium enolates from amides [8] and *cis* lithium thioenolates [9a,b] from thioamides. This selectivity has been exploited in sterospecific aldol reactions [10]: *syn* aldols [11] are derived from *cis* enolates and *anti* aldols from *trans* enolates.



Thioenolization of dithioesters has been already reported mostly in protic conditions. The resulting thioenolates were S-alkylated by alkyl halides [12], and in the particular case of dithioacetates condensed with aldehydes [13] (C addition). However the stereochemistry of this deprotonation has not been yet studied and can not be easily anticipated from the known kinetic enolizations . Dithiopropanoates were deprotonated under kinetic conditions : THF, LDA. Deprotonation was effective for each dithiopropanoate at -78°C as shown by analyzing S-alkylation products formed by alkylation of lithium thioenolates with alkyl iodides. In each case a mixture of isomeric ketene dithioacetals was isolated, which ratio was determined by G.C. [14]. Then following cross reactions were conducted assuring us that alkylation was entirely stereospecific

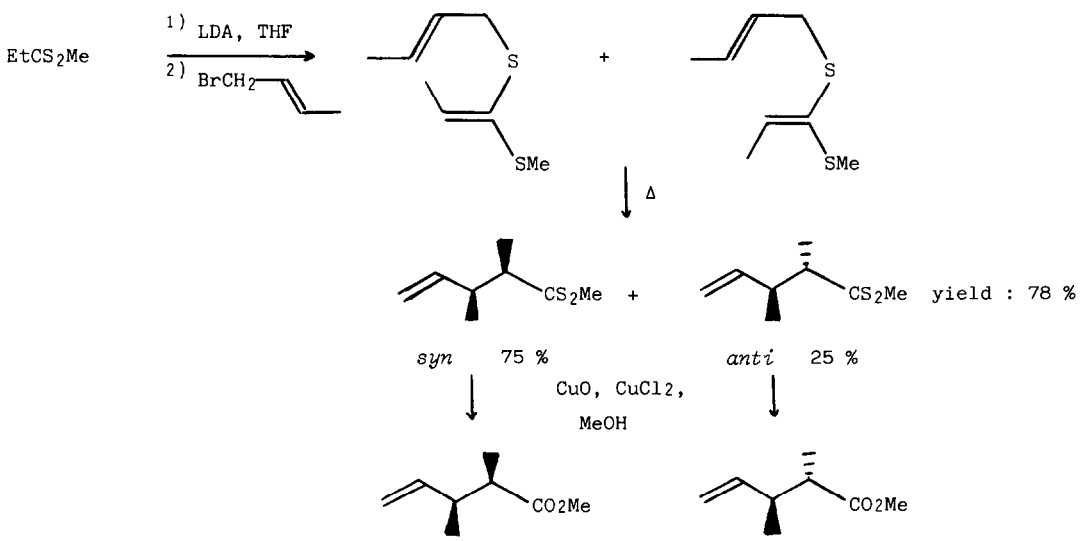


R^1	R^2	alkylation conditions	Yield *	ratio A/B * *
Et	Me	-78°C, 15 mn	89 %	70/30
Me	Et	-78°C to + 20°C, 1 h	81 %	24/76
iPr	Me	-78°C, 15 mn	71 %	81/19
Me	iPr	-78°C to + 20°C, 1 h	79 %	26/74

* distilled product

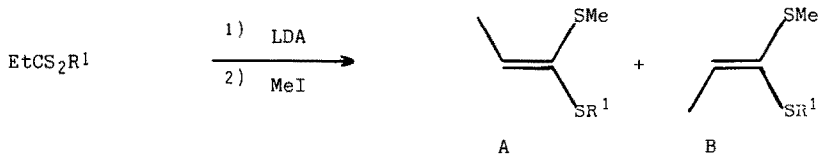
* * determined by GC. A is the first eluted product.

In each couple of reactions, inverted ratios of isomeric alkylated products are observed, proving that there is no isomerization of thioenolates. As seen from the table the formation of one isomer is favoured. Its geometry was established using the thio-Claisen rearrangement. In such a [3,3] sigmatropic rearrangement the geometry of products is directed by the configuration of starting compounds [15] as illustrated by Ireland in his pioneering study of ester enolate rearrangement [4] and by Sucrow [16] and Yoshida [9b] in the case of amide enolates and thioamide thioenolates. S-allyl ketene dithioacetals are reported to undergo rearrangement under mild conditions giving γ-unsaturated dithioesters whose stereochemistry was not studied [17].



The mixture of the two kinetically formed lithium thioenolates of methyl dithiopropanoate was alkylated by (*E*)-crotyl chloride (-78°C to -30°C, 2 hours). As the rearrangement of the resulting acetals was not totally effective at room temperature, it was completed by heating during two hours at 100°C in methylcyclohexane. A mixture of the two expected dithioesters, separated by M.P.L.C. [18], was obtained in a ratio 75/25 (yield : 78 %) and transformed without any epimerization in the known methyl esters by treatment with CuO, $CuCl_2$ in a water-methanol (1/99) solution [19]. The major and minor methyl esters obtained were respectively identical with the *syn* methyl 2,3-dimethyl-4-pentenoate and the *anti* methyl 2,3-dimethyl-4-pentenoate prepared according to Ireland's procedure [4, 20]. From the ratio (75/25) of the two dithioesters formed by thio-Claisen rearrangement, very close to the 74/26 and 76/24 ratios observed for the ketenedithioacetals and then for the thioenolates, it was concluded that the major lithium thioenolate has the *cis* geometry.

Then we looked at the influence of the alkylthio group to improve this selectivity.



entry	R^1	ratio A/B
a	Et	70/30
b	iPr	81/19
c	tBu	84/16
d	$C(Me_2)Ph$	84/16
e	CH_2 OMe	86/14
f	Ph	87/13

The cis selectivity increases with the size of the alkylthio group (see entry a - d) and with the ability of the alkylthio group to chelate the lithium cation (entry e and f).

From this study, in contrast with the trans kinetic deprotonation of esters [4, 5] and thiolesters [8], *a favoured cis kinetic thioenolization of dithioesters* was observed. We are now studying other thiocarbonyl compounds such as thionesters and thioketones to determine if this *cis* deprotonation trend is typical of the thiocarbonyl function. We will also exploit this *cis* selectivity for the stereoselective synthesis of *syn* natural aldols and thio-Claisen rearrangement.

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