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DIASTEREOSELECTION IN THE REACTIONS OF THIOALLYLIC ANIONS WITH BENZALDEHYDE

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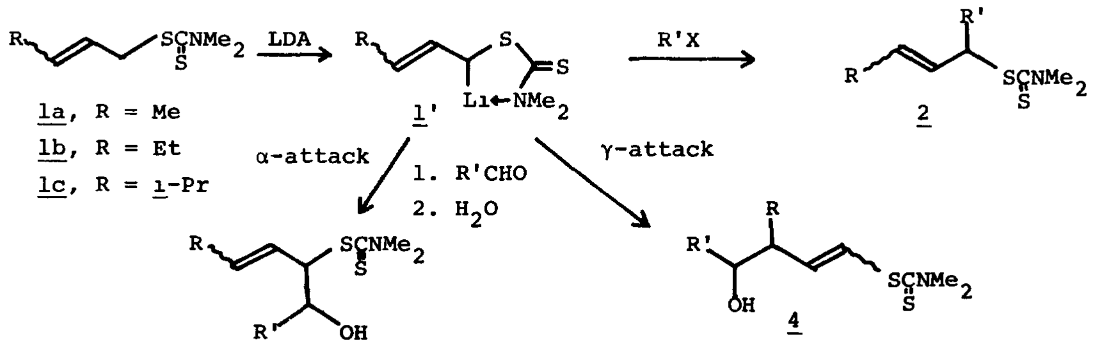
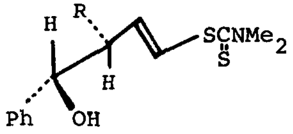
Summary: Reactions of the anions of (Z)-2-alkenyl N,N-dimethyldithiocarbamates with benzaldehyde gave the erythro isomers of 4-hydroxy-4-phenyl-(E)-1-alkenyl N,N-dimethyldithiocarbamates stereoselectively, and those of the anions of (E)-2-alkenyl N,N-dimethyldithiocarbamates afforded the threo isomers predominantly.

In the preceding communications[3] we reported that the lithium salt of allylic N,N-dimethyldithiocarbamates (1) are attacked by alkyl halides exclusively in the α-position. On the contrary, in the reactions of the anions (1') with carbonyl electrophiles we have observed that the product ratio α/γ was opposite to what one would predict based upon the above alkylation study (Scheme 1).[4] Although this change in α/γ regioselectivity in the reactions of unsymmetric allylic carbanions with carbonyl partners in contrast to alkyl halides was observed and discussed in a number of allylic systems,[5] little attension is so far paid to a stereochemical aspect of this reaction. Thus, the present studies were undertaken to elucidate whether both possible diastereoisomers will be formed and, if so, which will predominate. Such information would be not only of intrinsic mechanistic, but also of synthetic interest for its potential utility to the stereoselective synthesis of the β-methyl alcohol units of macrolide antibiotics.[6]

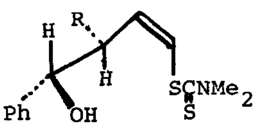


Scheme 1

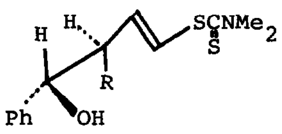
(E)-2-Alkenyl N,N-dimethyldithiocarbamates [1(E)] used in the present work were prepared according to the method described before[3] and (Z)-2-alkenyl N,N-dimethyldithiocarbamates [1(Z)] were derived from propargyl alcohol via several steps.[7] Reactions were carried out by preforming the lithium salt of 1 in THF by the addition to a THF/hexane solution of lithium diisopropylamide(LDA) at -60°. After the solution was cooled to -90°, benzaldehyde was added slowly to the rapidly stirring carbanion solution. The reaction mixture was quenched by addition of saturated aqueous NH_4Cl solution after red color of the solution disappeared. After separation of the layers, the aqueous layer was extracted with ether and the combined layers were washed with water, dried (anhydrous $MgSO_4$), and evaporated to afford an isomeric mixture of dithiocarbamates(3 and 4) in high yield. The product 4 consisted of a stereoisomeric mixture of four isomers, that is, *threo*-(E), *threo*-(Z), *erythro*-(E), and *erythro*-(Z), as depicted below, which could be separated into pure form with the use of a preparative liquid chromatography(PLC).[8] The relative configuration of each isomer of 4 was determined by correlating it chemically with β-hydroxy esters of known configuration.[9] The geometric configuration about the newly formed double bond was determined from the olefinic proton signals in the nmr spectra, using the well-established fact that $J_{trans} > J_{cis}$.[10] Once the configurations of all the isomers are determined, the isomeric ratios of 4 can be evaluated from the crude products by the use of nmr and high-pressure liquid chromatography(HPLC). The results are listed in Table 1.



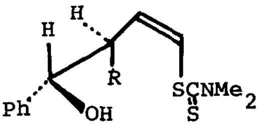
4-*threo*-(E)



4-*threo*-(Z)



4-*erythro*-(E)



4-*erythro*-(Z)

Table 1. Regio- and Stereoselectivities in Reactions of 1' with Benzaldehyde

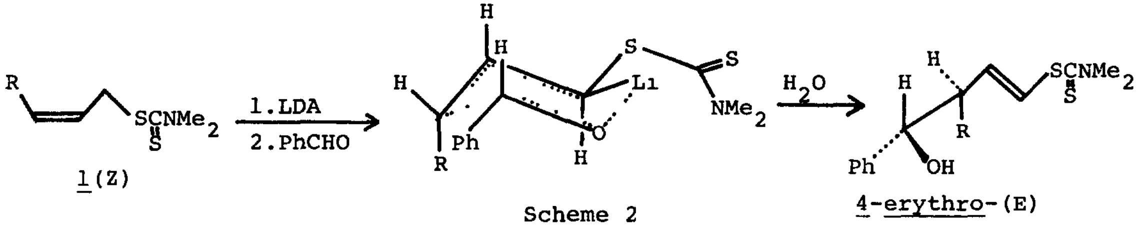
Anion 1'	R	Yield of[a] 3 + 4 (%)	γ/α ratio	Isomer Ratio of 4 *threo*(E)	*threo*(Z)	*erythro*(E)	*erythro*(Z)
1'a(Z)	Me	85	9:1	11.0	0	89.0	0
1'b(Z)	Et	84	9:1	8.0	0	92.0	0
1'a(E)	Me	92	9:1	50.7	7.2	23.7	18.4
1'b(E)	Et	87	9:1	53.6	2.6	25.1	18.7
1'c(E)	i-Pr	85	9:1	74.6	7.1	9.8	8.5

[a] Combined isolated yield based on the dithiocarbamate 1 used.

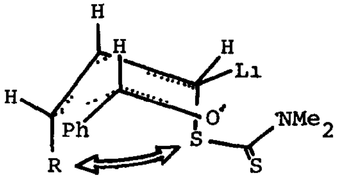
Table 2. NMR Data of $PhCH_{\underline{a}}(OH)CH_{\underline{b}}RCH_{\underline{c}}=CH_{\underline{d}}SCSNMe_2$

	$J_{\underline{ab}}$(Hz) threo	$J_{\underline{ab}}$(Hz) erythro	$J_{\underline{cd}}$(Hz) E	$J_{\underline{cd}}$(Hz) Z
4a	7.6	4.8	15.6	9.6
4b	7.5	5.2	15.8	9.6
4c	7.9	6.0	15.4	9.6

It was confirmed that the reactions were kinetically controlled, and that no isomerization of the anions (1') occurred. Table 1 shows that the reactions of 1' having E configuration with benzaldehyde afforded only a slight excess of 4-threo isomers, when R = Me and Et. However, this threo-selectivity was much enhanced by the bulkier alkyl substituent (R = i-Pr). On the other hand, the reactions of 1' having Z configuration with the aldehyde gave the erythro isomer stereoselectively. The high erythro-selectivity of 1'(Z) observed is in contrast to a much lower threo-selectivity of 1'(E). Furthermore, it should be noticed that the reaction of 1'(Z) led to the exclusive formation of the E forms, whereas that of 1'(E) yielded significant amounts of the Z forms. Recently, stereoselectivity of the aldol condensations was explained by assuming a six-centered chair conformation transition state.[6a, 11] An analogous transition state, as depicted below, may be applied to the reactions leading to the erythro isomers from 1'(Z).[12] The strong preference for a chair conformation transition state explains both exclusive formation of the E forms as well as diastereoisomeric induction (Scheme 2 and 3). However, the low stereoselectivity observed in the reactions of 1'(E) cannot be explained fully at the present time. The change of a counterion from lithium to zinc or magnesium made no difference in regioselectivity. This contrasts with the well-known facts that the regioselectivity of reactions of allylic anions with carbonyl electrophiles are drastically counterion dependent.[5d-f] In conclusion, the erythro-selectivity of the reactions is high enough to be used for the stereoselective synthesis of the β-methyl alcohol units, which fortunately have all erythro configuration in macrolide antibiotics. In order to enhance the stereoselectivity, further studies are continuing.



Scheme 2



Scheme 3

References and Footnotes

(1) Presented at part at the ACS/CSJ Chemical Congress, Honolulu, Hawaii, U.S.A. April (1979).

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(7) Propargyl tetrahydropyranyl ether was alkylated in the usual way and then hydrogenated in the presence of the Lindlar catalysis to give (Z)-2-alkenyl tetrahydropyranyl ether. After hydrolysis of the ether, brosylation of the alcohol, followed by the treatment with sodium N.N-dimethyldithiocarbamate in DMF at room temperature gave (Z)-2-alkenyl dithiocarbamate [1(Z)].

(8) All compounds were obtained as yellow oil, except for **4a**-*erythro*-(E)(mp, 65-68°), **4c**-*threo*-(E)(mp, 96-99°), and **4c**-*threo*-(Z)(mp, 105-110°). The combustion analyses of the compounds were all in good agreement with the calculated values.

(9) Ozonolysis of **4**, followed by oxidative work-up, afforded the β-hydroxy acid, which was treated with diazomethane to give the β-hydroxy ester, of which stereochemistry was studied in detail; a) J.Canceil, J.J.Basselier, and J. Jacques, Bull. Soc. Chim. France, 1024 (1967); b) J.Canceil and J.Jacques, ibid, 2180 (1970).

(10) H.B.Kagan, Stereochemistry, vol.1, p.45, Georg Thieme, Stuttgart (1977).

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(12) A discussion of the possibility that the reaction of thioallylic anions with aldehyde goes through a six-centered cyclic transition state, is given in the following papers; a) P.M.Atlanti, J.F.Biellmann, S.Dube, and J.J.Vicens, Tetrahedron Lett., 2665 (1974); b) E.Block, Reactions of Organosulfur compounds, p. 71, Academic Press, New York (1978).

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