Tetrahedron Letters,Vol.25,No.41,pp 4655-4658,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

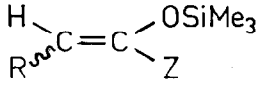
KETENE BIS(TRIMETHYLSILYL) ACETALS. CROSS-ALDOL CONDENSATION WITH ALDEHYDES. STEREOCHEMISTRY OF THE REACTION

Jacques-Emile DUBOIS*, Georges AXIOTIS and Emmanuel BERTOUNESQUE
Institut de Topologie et de Dynamique des Systèmes de l'Université Paris VII (associé au C.N.R.S), 1, rue Guy de la Brosse, 75005 Paris (France).

The titanium tetrachloride catalyzed condensation of the title acetals with aldehydes, leads to threo or erythro β-hydroxyacids with good stereoselectivity which depends mainly on the nature of the acetal counterion.

The stereoselective synthesis of aldols is a challenging problem in synthetic organic chemistry. It is now well established that diastereoselective kinetic aldol condensation can be carried out with preformed enolates. Our first investigations in the field of metal enolates[1] have been greatly extended by numerous research groups[2]. There is no doubt that kinetic diastereoselectivity depends upon the geometry of the enolate double bond[3] (E enolates giving, generally, threo aldols and Z enolates erythro products), the nature of enolate substituents and, to a minor extend, upon this of the aldehyde[2]. The most popular transition state which, in most cases, accounts for stereoselectivities observed is the chair or its diastereomeric boat six-membered ones, where the metal counterion can chelate the two oxygen atoms[2].

Nevertheless, such generalizations seem less evident with silicon enolates 1, as there are scattered reports dealing with the stereoselectivity of these Lewis acid catalyzed processes and, "a detailed analysis of this reaction in terms of probable transition states awaits further investigations"[2b]. As an example, it is worth mentioning that the Z enolsilane of t-butyl ethylketone (1c, R=Me, Z=t-Bu), when condensed with aldehydes is anti selective with boron trifluoride etherate as catalyst[2c] and syn selective with fluorine ion catalysis[4]. In some other cases, a single diastereoisomer is obtained regardless to the stereochemistry of the enolsilane double bond[5]. Related reactions concerning the condensation of Z and E enolsilanes of ethyl propionate (1a, R'=Et, R=Me) with aldehydes catalyzed by titanium tetrachloride, have been reported by Chan et al.[6]. Both stereoisomers show an anti selectivity, the magnitude of which is greater with the E isomer.



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1a : Z = OR' (R' = alkyl)

1b : Z = $OSiMe_3$

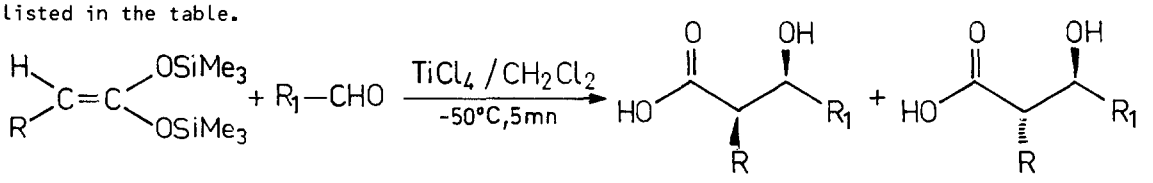
1c : Z = alkyl

In view of these results, it might be tempting to infer that the double bond geometry of

enolsilanes 1 does not govern the stereochemistry of aldol condensation products.

We recently reported for the first time[7], that compounds 1b, structural analogous of acetals 1a[6,8], add to aldehydes and Schiff bases in a cross-aldol type condensation, to afford β-hydroxyacids and β-lactams respectively, with good yields. Continuing our investigations in this field, we report in this paper the stereochemical outcome of the reaction of enolate prochiral equivalents 1b with aldehydes in the presence of titanium tetrachloride. This study makes it possible to examine the stereoselectivity of this reaction solely as a function of R and R_1 groups (see scheme), since compounds 1b (closely related to carboxylic acid dianions reported, inter alia, by Mülzer[9]), present no geometrical isomerism.

Compounds 1b[10] were condensed with various aldehydes R_1CHO in dichloromethane at -50°C according to our previously described procedure[7]. After 5 min[11], the mixture was treated as indicated and the crude practically pure product was subjected to a silica gel filtration to provide the mixture of the two isomers of erythro 2 and threo 3 β-hydroxyacid. The results obtained are listed in the table.



1b 2 ERYTHRO 3 THREO

S C H E M E

T A B L E : Condensation of acetals 1b with aldehydes R_1CHO

ENTRY	R	R_1	YIELD[a] (%)	RATIO 2 : 3[b]
1		Ph	90	77 : 23
2	t-Bu	t-Bu	85	89 : 11
3		Et	70	70 : 30
4		Ph	91	30 : 70
5	Ph	t-Bu	88	45 : 55
6		Et	75	15 : 85
7	Me	Ph	91	14 : 86
8		t-Bu	88	11 : 89

a) Non optimized yields in pure isolated products (mixture of the two diastereoisomers).
b) Determined by proton NMR analysis at 100 MHz, in acetone. All δ and J values are in agreement with those reported by Mülzer[9] for the same products.

All reactions proceed with good diastereoselectivity (except one case, entry 5 of the table). With R = Me, Ph, the threo hydroxyacid 3 is obtained predominantly while the oposite diastereoisomer 2 is observed with the bulky t-Bu group. Such behaviour, where there is a reversal of diastereoselectivity with bulky groups, has been noted, inter alia, by us[1b] in the case of metal enolates and by Evans[12] in the condensation of structural analogues to 1b diboryl enediolates with aldehydes. It represents another example of a stereochemical crossover observed with sterically demanding groups on the enolate counterion. It is noticeable that in this case, our reaction leads to the opposite diastereoselectivity of that obtained by Mülzer's carboxylic acid dianions[9] and consequently, affords a complementary method for selective diastereoselectivity. Good selectivity is obtained even with R = Me in 1b (entries 7 and 8 of the table), while Mülzer's method is stereorandom in these cases[9]. Previous observations, which are also confirmed in these cases, indicate that the nature of R_1 group of the aldehyde does not significantly affect the selectivity of the reaction[2].

For selectivities observed it is difficult to put forward an explanation in terms of plausible transition states. We think that chelated six-membered transition states are not totally adequate as they take into account the double bond geometry of the enolate, non existent in the case of our enolates 1b, and, do not consider the eventuality of aggregation phenomena which would complicate stereochemical considerations. Our remark is reinforced by the fact that Chan has observed a threo diastereoselectivity with both geometrical isomers of trimethylsilyl propionate (1a, R'=Et, R=Me) with aldehydes, in the presence of titanium tetrachloride[6]. The same remarks have been recently pointed out by Gaudemar et al.[13] with the analogues to 1b (Z) N,N-dimethyl S-trimethylsilyl ketene acetals. Unfortunately, they did not report on the E isomers and thus we cannot assert if the same or the reverse selectivity would be obtained. To complete Chan's observations, we performed the condensation of both Z and E isomers of O-ethyl O-trimethylsilyl t-butylketene acetal (1a, R'=Et, R=t-Bu)[14] with benzaldehyde under his conditions (-78°C, 30 min). With both isomers we observed the opposite selectivity (>92% erythro)[15] than that observed by Chan with ethyl propionate enol ether[6]. This fact is in agreement with the reversal of selectivity we observe with our products (entries 1 to 3 of the table) and reinforces our hypothesis about the minimal influence of the enolate double bond geometry on stereoselectivities.

All these observations prompted us to infer that six-membered chelated transition states could not alone explain the selectivity of the reaction of 1b and consequenly, the analogous 1a or thioamide acetals[13], as is pertinently observed by Gaudemar for his related reactions. More detailed studies concerning our reaction are necessary to determine the factors controlling the stereochemistry of this aldol condensation process. The problem seems more complex than can be solved by hypotheses formulated[6] with closely related compounds 1a and which can be limited to steric factors associated with the enolate geometry at the level of interaction in the transition state.

In conclusion, we have shown that compounds 1b permit a stereoselective synthesis of β-hydroxyacids with good yields. The selectivity of the reaction depends on the nature of the substituents of 1b. So, with relatively small groups the threo isomer predominates, while the opposite selectivity is observed with bulky groups. Selectivities are not obviously rationalized by classical transition state models. Spectroscopic considerations are under investigation to try to determine the mechanistic outcome of these reactions.

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15. PhCHOHCH(t-Bu)COOEt (erythro), isolated as 100% pure by preparative V.P.C on a SE 30 column. I.R (neat): 3500, 3055, 1730, 700; N.M.R. ($CDCl_3$): 0.87 (t,3,Me), 1.16 (s,9,t-Bu), 2.68 (d, 1,CH-CO, J = 10.2 Hz), 3.73 (q,2,CH_2), 4.96 (d,1,CH-OH, J = 10.2 Hz), 7.30 (m,6,$H_{arom.}$ and OH).

(Received in France 26 July 1984)