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STEREOSELECTION IN THE CONDENSATION BETWEEN ETHYL PROPIONATE AND ALDEHYDES[1]

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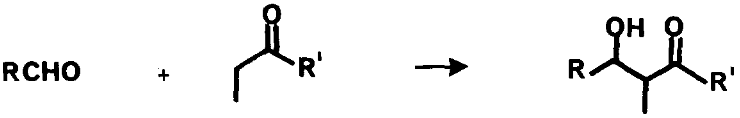
Summary: *Ethyl propionate can be converted stereoselectively into geometrical isomers of O-ethyl-O-trimethylsilylmethylketene acetal (5). The E-isomer of 5 condenses with aldehydes by titanium tetrachloride to give stereoselectively the threo isomers of ethyl 2-methyl-3-hydroxy carboxylates.*

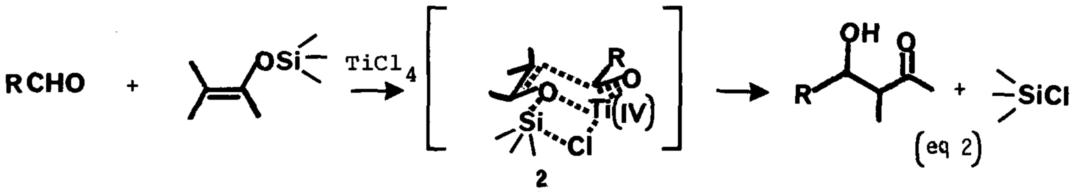
The stereoselective synthesis of acyclic systems in a cross-aldol type condensation (equation 1) is a problem of pressing concern in organic synthesis. It is a question of fundamental interest because aldol-type condensations are used often in biological systems as an effective way of forming new carbon-carbon bonds. The aldol condensation will be extremely useful to the synthesis of a number of natural products, provided that the stereochemistry of the condensation reaction can be controlled. An important extension of the stereoselective aldol-type condensation is the synthesis of 2-methyl-3-hydroxycarboxylic acid (1, R' = OH) which is the structural unit common to many natural products (e.g. methymycin). Some approaches to this problem have been presented by Heathcock[2,3] and Ireland[4].



(eq 1)

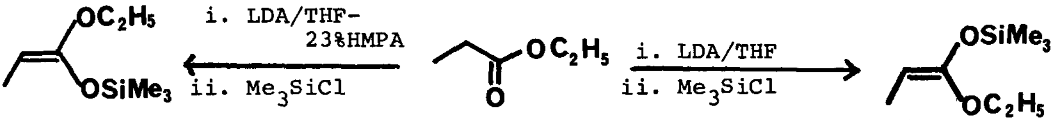
1

It seems to us that two requirements must be met before high stereoselection can occur. The first is that the enolate or its equivalent must retain its geometry during reaction. The other is that a cyclic transition state must be involved. Both those conditions can perhaps be satisfied by the reaction of enol silyl ethers with carbonyl compounds using titanium tetrachloride as the catalyst (equation 2). Geometric isomers of enol silyl ethers can now be prepared from the acyclic carbonyl precursors[4,5]. While the exact mechanism of the titanium tetrachloride promoted cross-aldol condensation is not known[6], it is possible that the reaction may proceed by a cyclic transition state 2 in view of the known affinity of titanium for oxygen[7] We wish to report here our study on the condensation of ethyl propionate 3 with aldehydes using such an approach.



(eq 2)

Ethyl propionate can be converted stereoselectively into geometrically pure Z-O-ethyl-O-t-butyldimethylsilylmethylketene acetal (4a)[4]. Efforts to obtain the E-isomer (4b) however was not successful[8]. On the other hand, both geometrical isomers of O-ethyl-O-trimethylsilylmethylketene acetal (5a and 5b) can be obtained in high isomeric purity (Scheme 1) . The stereochemistry and the ratio were deduced from the nmr spectra by using the resonance signals of the vinyl protons[9].



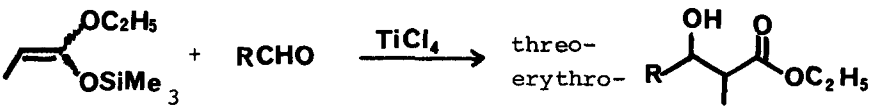
5a (E/Z=0/100)

3

5b (E/Z=85/15)

Scheme 1

When either 4 or 5 is condensed with an aldehyde using titanium tetrachloride in methylene chloride, the product 6 , a mixture of threo and erythro isomers, can be obtained in good yield (Table). The diastereomeric structures were determined from the carbinol resonances in the ^{1}H nmr spectra[10]. The diastereomers are also separable by gas chromatography[11] and their ratio deduced.



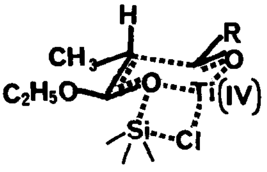
5a or 5b

6

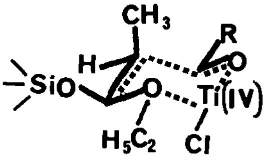
It is clear from the Table that the E-isomer 5b condenses with aldehydes to give stereoselectively the threo isomer. Stereoselectivity improves with lower reaction temperature. The R group of the aldehyde appears to have some effect also, with the bulkier isopropyl group giving the highest threo/erythro ratio. At the optimum temperature of -78°, it is possible to obtain the threo-isomer 6 (R = i-Pr) almost exclusively.

On the other hand, the condensation of an aldehyde with the Z-isomer (either 4a or 5a) proceeds with little stereoselectivity or with slight preference for the threo diastereomer.

While the precise mechanism of the reaction is not known, the possibility of a titanium enolate as the intermediate in these reactions can be ruled out. This is based on the observations that titanium tetrachloride must be premixed with the aldehyde before the addition of the ketene acetal. Otherwise the yield of 6 is much diminished. We also find that when E-O-ethyl-O-trimethylsilylmethylketene acetal (5b) is mixed with titanium tetrachloride, an equal mixture of meso and dl-diethyl 2,3-dimethylsuccinate is obtained[12], products otherwise not observed in the condensation reaction. As a working hypothesis, we feel that the transition states 7a and 7b with chair-like structure and the R group equatorial may adequately account for the stereoselection of the reaction. Two factors, the equatorial methyl and a stronger O-titanium bond because of a weakened O-silyl bond, render 7a a lower energy transition state than 7b. The product is therefore stereoselectively the threo isomer. If this hypothesis is correct some obvious modifications suggest themselves in order to obtain the erythro isomer. We are now working in this area.



7a

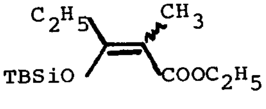


7b

Acknowledgement We wish to thank National Science and Engineering Research Council of Canada and the Ministry of Education, Government of Quebec for financial support of this research.

References and Footnotes

1. Chemistry of Enol Silyl Ethers, Part III. For part II, see T.H. Chan and P. Brownbridge, to be published.
2. W.A. Kleschide, C.T. Buse and C.H. Heathcock, J. Amer. Chem. Soc., 99, 247 (1977).
3. C.T. Buse and C.H. Heathcock, J. Amer. Chem. Soc., 99, 8109 (1977).
4. R.E. Ireland, R.H. Mueller and A.K. Willard, J. Amer. Chem. Soc., 98, 2868 (1976).
5. E. Nakamura, K. Hashimoto, I. Kuwajima, Tetrahedron Letters 2079 (1978).
6. K. Saigo, M. Osaki, T. Mukaiyama, Chem. Lett. 989 (1975).
7. J.E. McMurray, Acc. Chem. Res., 7, 281 (1974).
8. The product obtained was identified to be 8, b.p. 120°/7 mm, in 40% yield.
9. ^{1}H Nmr data for O-silylketene acetals (in CCl_4): 4a: 1.45(d,3H), 3.29(q,1H), 3.65(q,2H), 1.25(t,3H), 0.12(s,6H), 0.93(s,9H); 5a: 1.43(d,3H), 3.28(q,1H), 3.35(q,2H), 0.99(t,3H), 0.19(s,9H); 5b: 1.43(d,3H), 3.58(q,1H), 3.25(q,2H), 1.18(t,3H), 0.19(s,9H).



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10. ^{1}H nmr data of the carbinol hydrogen in compound 6: 6a(R'=C_2H_5, R=iPr): threo: 3.18(dd, J=6.0 Hz), erythro: 3.39(dd, J=3.5 Hz); 6b(R^1=C_2H_5, R=n-C_5H_{11}): threo: 3.53(m), erythro: 3.75(m); 6c(R^1=C_2H_5, R=C_6H_5: threo: 4.55(d, J=8.0 Hz); erythro: 4.90(d, J=4.0 Hz).

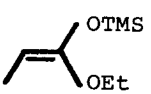
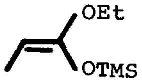
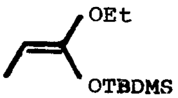
11. For determination of isomer ratio by GC: Aerograph 700 gas chromatograph with polydiethyleneglycol succinate (10%) on chromosorb-W in 2 m alumina column is used.

12. S. Inabe and I. Ojima, Tetrahedron Letters, 2009 (1977).

13. After submission of this paper, two reports on this topic have appeared: A. I. Meyers and P.J. Reider, J. Amer. Chem. Soc., 101, 2501 (1979); M. Hirama and S. Masamune, Tethedron Lett., 2225(1979). The latter approach using vinyloxyboranes shows superior stereoselection.

TABLE

Yields and Diastereomeric Ratios of Products 6 in the Condensation of O-Silylketene Acetal with Aldehydes.

O-Silylketene acetals	Aldehydes RCHO	Reaction Conditions T°(C),	Time (hrs)	Yield (%)[a] of 6	threo/erythro of 6
 5b	R = 	-78	0.5	75	100/~0[b]
		-20	0.5	73	84/16[b]
		+10	0.5	74	74/26[b]
	R = 	-78	0.5	77	94/6[b,c]
	R = Ph	-78	0.5	79	75/25[b]
 5a	R = 	-78	0.5	77	52/48
		+10	0.5	75	50/50
	R = 	-78	0.5	77	53/47[c]
	R=Ph	-78	0.5	78	67/33
 4a	R = 	-78	0.5	78	61/39
		+10	0.5	78	50/50
		+40	0.5	not determined	50/50
	R = 	-78	0.5	76	62/38
	R = Ph	-78	0.5	78	67/33

a. Isolated yield

b. Corrected value for the presence of 15% Z isomer in starting material

c. The ratio was determined by VPC[11].

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