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ACID CATALYSIS IN ALDOL CONDENSATION OF α-AMINO SILYL KETENE ACETALS. DIASTEREOSELECTIVE SYNTHESIS OF α-AMINO-β-HYDROXYACIDS.

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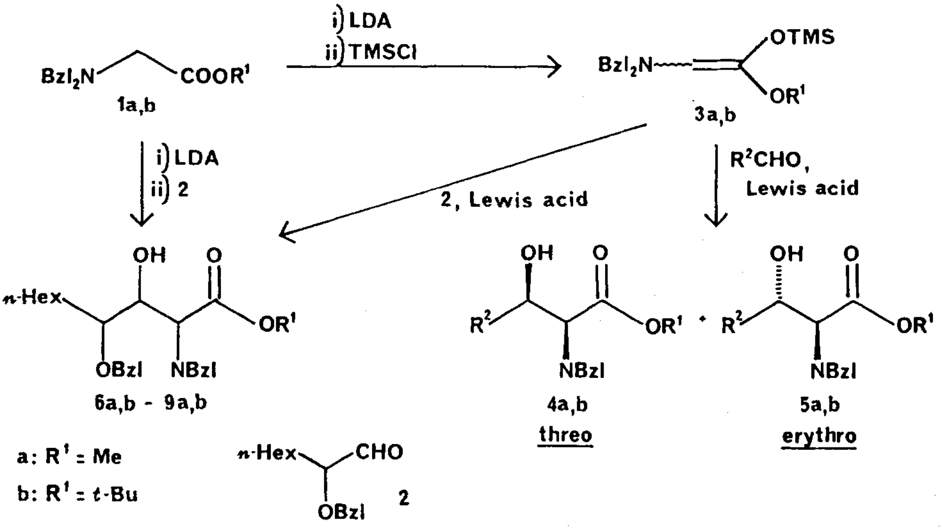
Summary: The aldol-type condensation between α-dibenzylamino trimethylsilyl ketene acetals and various achiral and chiral aldehydes in the presence of a Lewis acid furnishes α-amino-β-hydroxyacids in moderate yields with preferential C_2-C_3 threo configuration.

Recently we reported the use of dibenzylaminoacetates 1 in the stereoselective synthesis of α-amino-β-hydroxyacids either via aldol condensation of the corresponding lithium enolates or through an acylation-reduction sequence.[1]



In the course of a project directed toward the stereoselective synthesis of amino sugars from non-carbohydrate precursors, we planned to extend the reported methodology[1] to the synthesis of β, γ-dihydroxy-α-aminoacids. However, of the two procedures previously described, the acylation-reduction one was ruled out since the acylation of 1 with an α-hydroxyacid derivative was expected to proceed with low diastereoselectivity.

Moreover, the aldol condensation between the lithium enolates derived from 1 and the model α-alkoxyaldehyde 2[2] gave a mixture of all possible isomers 6-9 with low stereoselectivity.[4] This result was not surprising, given the low "internal asymmetric induction"[5] obtained in the reaction of these enolates with achiral aldehydes[1] and the low "relative asymmetric induction"[5] usually achieved with lithium enolates.[6]

On the contrary the acid catalyzed condensation of silyl enol ethers with α-alkoxyaldehydes is known to often proceed with good to excellent "relative asymmetric induction".[5]

However, in spite of a large amount of results on the reaction between carbonyl compounds and silyl enol ethers,[7] little has been reported on the related reaction with silyl ketene acetals[8] and even less dealing with the acid catalyzed aldol reaction of α-hetero substituted derivatives.

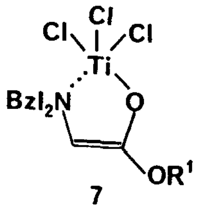
In order to explore this new interesting field we synthesised the α-dibenzylamino-O-trimethylsilylketene acetals 3a,b according to known procedures[9] (LDA, -78°C, then Me_3SiCl) and examined their behaviour toward a series of aldehydes.

In all cases only one geometric isomer of 3a,b was detected. Although it was not possible to determine unambigously the configuration of these products, we guess that the configuration should be Z due to the stabilisation of the E enolate[10] by coordination of lithium with the amino group.[3]

The internal asymmetric induction[5] of acid catalysed aldol condensation was tested in the reaction of methyl and t-butyl trimethylsilyl ketene acetals 3a and 3b with a series of achiral aldehydes in the presence of various Lewis acids. Representative results are listed in table 1. A crucial point is represented by the order of mixing of the reactants with the catalyst. For example when 3a was treated with $TiCl_4$ and then the aldehyde was added or when $TiCl_4$ was added to a mixture of aldehyde and 3a no reaction occurred at all except when a large excess of acetaldehyde was used.

In analogy with the behaviour of enol silyl ethers[2] 3 should form, by reaction with $TiCl_4$, a trichlorotitanium enolate 7, which appears to dimerize giving succinates,[8a,b] rather than to react with aldehydes.

Optimal conditions seem to be pre-mixing the Lewis acid with a 4-fold excess of aldehyde and then adding a CH_2Cl_2 solution of 3a or 3b (1 eq. with respect to Lewis acid). This procedure was applied in all the entries of table 1.



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When R^1 = Me, however, yields were still unsatisfactory because of the formation of succinates as by products in considerable yields.[8a,c] The diastereoselectivity was also low.

The yields could be improved by using t-butyl trimethylsilyl ketene acetal 3b and by increasing the temperature of addition of the latter. Indeed best results were obtained when $TiCl_4$ and the aldehyde were mixed at -78°C, the temperature was suddenly raised to 20°C and 3b was finally added at this temperature. Under these conditions the diastereoisomer ratio was moderate to good[11].

The examination of Table 1 indicates in every case the predominant formation of threo isomers 4. This result is not surprising, if the silyl ketene acetal with Z configuration is involved either in Zimmerman-Traxler cyclic model or in an acyclic model.[6]

Finally we applied the same procedure to the alkoxyaldehyde 2 (Table 2). Again methyl derivative 3a gave very low chemical yields. On the contrary, t-butyl compound 3b gave acceptable chemical yields but only modest stereoselectivity. In the best case, one of the four diastereoisomers constituted 59% of the total mixture. This is an intriguing result, compared with literature reports,[7,8,12] quoting for generally low internal asymmetric induction with achiral aldehydes[7,8d] but high relative and internal asymmetric induction with alkoxy- aldehydes.[8e,12]

In our opinion, this unexpected behaviour of 3a and 3b could be due to the presence of the dibenzylamino group, which could coordinate the Lewis acid as well and make transition states more complex than previously proposed for non-hetero substituted silyl ketene acetals.[8e,13,14]

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Table 1

Entry	R^1	R^2	Lewis acid	T/°C	Yield/%[a]	Ratio 4:5[b]
1	Me	Me	$BF_3.Et_2O$	-65	15	64:36
2	Me	Me	$SnCl_4$	-65	14	55:45
3	Me	Me	$TiCl_4$	-65	17	44:56
4	t-Bu	Me	$TiCl_4$	-65	20	85:15
5	t-Bu	Me	$TiCl_4$	r.t.	47 (55)	70:30
6	Me	n-Hex	$TiCl_4$	r.t.	24	54:46
7	t-Bu	n-Hex	$TiCl_4$	r.t.	56	85:15
8	t-Bu	n-Hex	$TiCl_4$	-20	29 (52)	91: 9
9	t-Bu	n-Hex	$TiCl_4$	-78	14 (21)	97: 3
10	t-Bu	t-Bu	$TiCl_4$	r.t.	45	91: 9
11	t-Bu	c-Hex	$TiCl_4$	r.t.	52	84:16
12	t-Bu	Ph	$TiCl_4$	r.t.	66	61:39

[a] Yields referred to isolated 2+3; yields based on unrecovered ester are reported in parentheses. Determined by t.l.c. spectrodensitometry (254 nm).

Table 2

R^1	Lewis acid	T/°C	Yield/%[a]	Ratio 6:7:8:9[b]
Me	$BF_3.Et_2O$	-65	13	22:32:16:31
Me	$SnCl_4$	-65	17	3:34:62: 3
t-Bu	$SnCl_4$	-78	53	25:59: 0:16
t-Bu	$TiCl_4$	-78	55	27:50: 7:16

[a] Yields referred to isolated 6+7+8+9. [b] Determined by t.l.c. spectrodensitometry (254 nm). The order of elution (n-hexane-Et_2O-AcOH 70:30:1) is 6, 7, 8, and 9.

References and notes.

1) G. Guanti, L. Banfi, E. Narisano, C. Scolastico, Tetrahedron Lett., 1984, 4693.

2) Synthesized in three steps from di-p-tolylthiomethane: i) n-BuLi, THF, n-HexCHO, 90%; ii) NaH, DMF, $PhCH_2Br$, 90%; iii) $HgO.BF_3$, THF-H_2O, 85%. Optically active 2 can be easily obtained by known procedure (G. Guanti, E. Narisano, F. Pero, L. Banfi, C. Scolastico, J.C.S. Perkin 1, 1984, 189).

3) L. Banfi, A. Bernardi, L. Colombo, C. Gennari, C. Scolastico, J. Org. Chem., 49, 3784 (1984).

4) R^1 = Me: yield 72%, 6a:7a:8c:9d = 35:15:20:30; R^1 = t-Bu: yield 81%, 6b:7b:8b:9b = 30:32:32:6.

5) P. A. Bartlett, Tetrahedron, 1980,3.

6) D. A. Evans, J. V. Nelson, T. R. Taber, Topics in Stereochemistry, 13, 1.

7) T. Mukaiyama, Org. Reactions, 1982, 203.

8) a) T. H. Chan, T. Aida, P. W. K. Lau, V. Gorys, D. N. Harpp, Tetrahedron Lett., 1979, 4029; b) I. Matsuda, Y. Izumi, ibid., 1981, 1805; c) G. Wenke, E. N. Jacobsen, G. E. Totten, A. C. Karides, Y. E. Rhodes, Synthetic Commun., 1983, 449; d) M.T.Reetz, K.Kesseler, A.Jung, Tetrahedron, 40, 1984, 4327; e) C.H.Heathcock, K.T.Hug, L.A.Flippin, Tetrahedron Lett., 1984, 5973.

9) R. E. Ireland, R. H. Mueller, A. K. Willard, J. Am. Chem. Soc., 98, 2868, 1976. However 3a,b were hydrolysed very quickly in the presence of moisture. So they were stored as argon flushed CH_2Cl_2 solutions.

10) Note that E/Z notations are reversed for corresponding lithium enolates and silyl ketene acetals.

11) Although it can be further increased by conducting the reaction at lower temperatures, this was accompanied by a drastic reduction of yields.

12) M. T. Reetz, K. Kesseler, A. Jung, Tetrahedron Lett., 1984, 729 and references therein.

13) E. Nakamura, J. Shimada, Y. Origuchi, I. Kuwajima, Tetrahedron Lett., 1983, 3341 and 3343.

14) Attempts to use O,O-bis-(trimethylsilyl)ketene acetals (see J. E. Dubois, G. Axiotis, Tetrahedron Lett., 1984, 2143) in this reaction resulted in non-analyzable mixtures.

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