Tetrahedron Letters,Vol.23,No.41,pp 4285-4288,1982 0040-4039/82/414285-04$03.00/0
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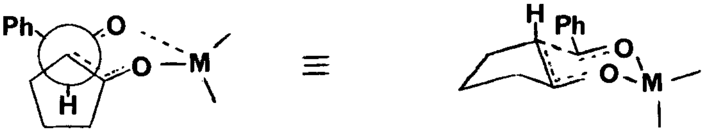
STEREOCONTROLLED ALDOL REACTIONS OF BUTYROLACTONE: ERYTHRO- SELECTIVITY VIA HIGH COORDINATION ZINC COMPLEXES

D.A. Widdowson*, G.H. Wiebecke and D.J. Williams
Department of Chemistry, Imperial College, London SW7.

SUMMARY: *The stereoselection of the lithium catalysed aldol reaction of benzaldehyde and γ-butyrolactone is reversed by zinc ions. The intermediacy of octahedral or square pyramidal zinc complexes is invoked to explain these observations.*

In connection with synthetic studies, we require 2-substituted butyrolactones. As a preliminary, we have examined the steric course of the aldol reaction of γ-butyrolactone and benzaldehyde[1] (Scheme) under a variety of conditions and catalysts. This has revealed a facet of stereocontrol,not previously reported, which promises to be of considerable use in substituted lactone synthesis.

In acyclic stereocontrolled aldol reactions, it is generally observed that E-enolates of lithium, magnesium, zinc and related metals give rise to predominantly threo products and Z-enolates to erythro products[2]. This situation can be reversed by other, usually bulky, counterions[3]. In cyclic systems, the enolate is necessarily of E-configuration and in cyclopentanones, the threo products predominate[4]. A chair-form cyclic transition state (as 1) has been used to explain these observations[2,4].



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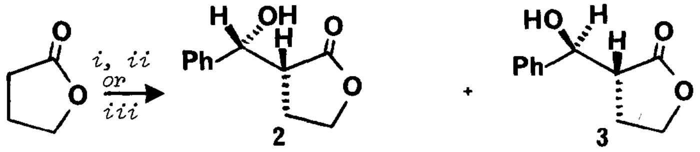
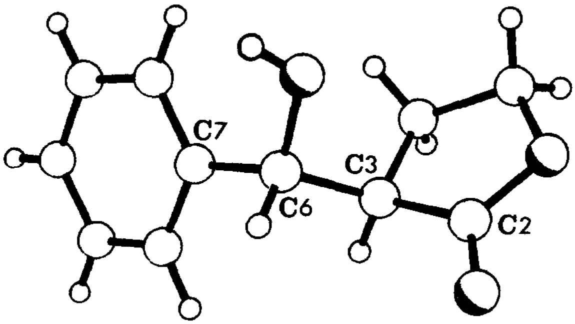
γ-Butyrolactone in THF was lithiated with LDA (1 equiv) at 20° during 2 h, cooled to -30° and benzaldehyde added slowly. After 1 h the reaction was quenched with phosphate buffer (pH 7), ether extracted, washed with aqueous sodium bicarbonate and brine, dried (Na_2SO_4) and concentrated to give the aldol product mixture, (2) and (3) Scheme.

Scheme



i, *LDA/THF*; *ii*, *PhCHO*; *iii*, $ZnCl_2$, *PhCHO*.

One of the diastereomers crystallised from the product mixture and in order to obtain an unambiguous assignment, an X-ray analysis was undertaken[5]. The crystalline diastereomer proved to be the erythro product (Figure).



Figure

The ratio of erythro (2) : threo (3) was determined by nmr spectroscopy. The benzylic protons resonated clear of all others at δ 5.35 (d, J 3 Hz) and δ 4.84 (d, J 8Hz) respectively. The results are given in the Table (Runs 1-3). At lower reaction temperatures, the product ratio maximised at (2) : (3) = 30 : 70, in parallel with the Dubois observations on cyclopentanone[4].

TABLE:

Run No.	Cation	Ratio (metal:lactone)	Temp. °C	Yield[a] (%)	Product Ratio (erythro:threo)
1	Li^+	1	-30°	74	41 : 59
2	Li^+	1	-78°	44	30 : 70
3	Li^+	1	-100°	21	30 : 70
4	Zn^{2+}	0.5	0°	86	63 : 37
5	Zn^{2+}	0.5	-30°	83	70 : 30
6	Zn^{2+}	0.5	-78°	73	56 : 44
7	Zn^{2+}	1	-30°	85	70 : 30
8	Zn^{2+}	0.1	-30°	48	54 : 46

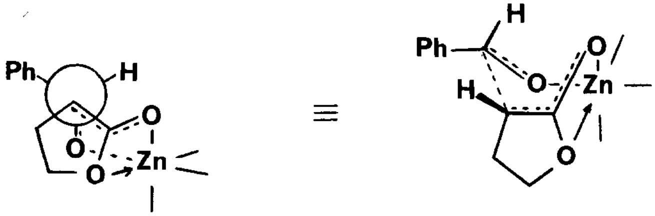
[a] *Combined yield, estimated by nmr. Only the erythro product was crystalline when pure.*

In the presence of 0.5 equivalents of anhydrous zinc chloride[6], enolate formation was accelerated (complete in 0.5 h at -78° → 20°) and the diastereoselection was reversed (Table, Runs 4-8). Increased proportions of zinc (Run 7) had no effect, but 0.1 equivalents (Run 8) gave reduced selectivity. The optimum reaction temperature proved to be -30°.

In a control experiment, a product mixture (erythro : threo = 30 : 70) was treated with LDA/ZnCl$_2$ under the reaction conditions (THF, -30°, 2h) and no equilibration was observed[7]. The zinc catalysed stereoselection is therefore kinetic in origin.

It is evident from the acceleration of enolate formation that a zinc enolate is being formed and that since 0.5 equivalents of zinc produce a maximum diastereoselection, control occurs via intramolecular coordination[8]. Since cation size (Li$^+$ ionic radius 0.78, Zn^{2+} ionic radius 0.69)[9] cannot be the source of selectivity, we propose that coordination geometry is the determining factor.

In contrast to lithium, zinc readily forms square pyramidal and octahedral complexes with oxygen ligands[10]. In a boat conformation of the transition state, as required for erythro-selection, the ring oxygen could act as a third ligand to square pyramidal or octahedral zinc, but is geometrically inhibited from doing so to lithium. The resulting stablished boat conformation is depicted in (4).



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The generality of this concept for other reactions with potential tri-coordination has yet to be determined, but could clearly be applied to ester enolates.

We thank the E.T.H., Zurich and Imperial College for an Undergraduate Exchange Studentship (to G.H.W.).

REFERENCES AND FOOTNOTES

1. The formation of methylene lactones by this route has been reported; P.A. Grieco, *Synthesis*, 1975, 67.

2. For extensive reviews, see P.A. Bartlett, *Tetrahedron*, 1980, **36**, 1; C.H. Heathcock, *Science*, 1981, 395.

3. D.A. Evans and L.R. McGee, *J. Am. Chem. Soc.*, 1981, **103**, 2876; Y. Yamamoto, and K. Maruyama, *J. Am. Chem. Soc.*, 1982, **104**, 232.

4. P. Fehlmann and J.E. Dubois, *Tetrahedron*, 1978, **34**, 1349.

5. Crystals of (2) are orthorhombic, a = 8.123(1), b = 9.764(1), c = 12.404(2) Å, U = 984 Å^3, space-group $P\,b\,n\,2_1$, Z = 4, D_c = 1.19 g cm^{-3}. Of the 701 independent reflections ($\theta \leq 58^{\circ}$) measured using Cu-K_{α} radiation, 5 had $|F_o| < 3\,\sigma\,(|F_o|)$ and were classed as unobserved. The structure was solved by direct methods and refined anisotropically to give R = 0.029. Coordinates for this work are lodged with the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. There is an intermolecular hydrogen bond (2.81 Å) between the hydroxy and carbonyl oxygens. Torsion angles: H-C(3)-C(6)-H 67°, C(2)-C(3)-C(6)-C(7) -173°.

6. H.O. House, D.S. Crumine, A.Y. Teranishi and H.D. Olmstead, *J. Am. Chem. Soc.*, 1973, **95**, 3310.

7. C.T. White and C.H. Heathcock, *J. Org. Chem.*, 1980, **45**, 1066.

8. *Erythro* selection could occur via reaction of the zinc enolate with zinc complexed benzaldehyde but this would have been enhanced by the higher zinc ion concentration in Run 7.

9. F.A. Cotton and G. Wilkinson, 'Advanced Inorganic Chemistry', 4th Ed., Wiley Interscience, 1980, p. 14.

10. For many examples see: O. Kennard, F.H. Allen and D.G. Watson in 'Molecular Structures and Dimensions, Guide to the Literature 1935-76. Organic and Organometallic Crystal Structures', Bohn, Scheltema and Holkema Publishing Corp., Utrecht, 1977.

(Received in UK 6 July 1982)