

Zinc Chloride induced Stereoselection in Syntheses of α -Amino- β -hydroxy Acid Derivatives

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Schiff bases formed from condensation of glycine esters with diphenylmethylenamine have been silylated followed by condensation with aliphatic and aromatic aldehydes at room temperature in the presence of catalytic amounts of ZnCl₂; the *syn*-condensation products are obtained in good yield and stereoselectivity, especially for aromatic aldehydes, and the sense of stereoselection reverses in the presence of stoichiometric or excess of ZnCl₂.

Because of the pharmacological and biological interest much effort has been expended the past twenty years in stereoselective syntheses of α -amino- β -hydroxy acids.¹ Glycine esters have often served as starting materials. For example, *N*-pyruvylidene-glycinato-copper(II) complexes,² *N,N*-bis-(trimethylsilyl)glycine trimethylsilyl ester,³ *N*-trifluoroacetyl glycine methyl ester,⁴ Ni^{II}⁵ and Zn^{II}⁶ chelate complexes of glycine Schiff bases, and dibenzylaminoacetates have been shown to react with aldehydes in diastereoselective and/or enantioselective syntheses of these acids.⁷

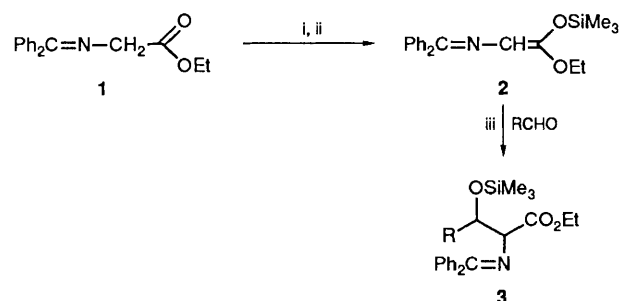
We describe here a procedure (Scheme 1) based on glycine esters for the synthesis of α -amino- β -hydroxy acid derivatives that affords for several important cases in high selectivity the *syn*† compounds, and provides, moreover, the possibility of reversal of stereoselection. In contrast to other methods, which are generally dependent on low temperature techniques, these reactions were carried out at room temperature unless otherwise noted.

The condensation of **2**, prepared by deprotonation of **1** with lithium diisopropylamide followed by quenching with excess of trimethylsilyl chloride,‡ with various aldehydes takes place in tetrahydrofuran (THF) solution containing ZnCl₂ (5% based on **1**) at room temperature (12 h). The products were

isolated by dilution with hexane and filtration over Celite, followed by chromatography with ether on silica. The isolated yields and diastereoselectivities are given in Table 1.

The chemical yields are generally satisfactory. However, for aliphatic aldehydes the diastereoselectivities are only modest except for bulky pivaldehyde (entry 4). The stereoisomers of **3e** were separated and *anti*- and *syn*-configurations were tentatively assigned on the basis of the magnitudes of the vicinal coupling constants of the protons attached to C-2 and C-3.⁸ *syn*-**3e** was degraded (2 mol dm⁻³ HCl, then NaOH for ester hydrolysis, then pH 7 to precipitate) to authentic phenylserine **4**. The stereochemical assignments to *syn*-**3e** based on coupling constants are confirmed by a crystal structure determination (Fig. 1).§

Diastereoselectivities are considerably higher for condensations with aromatic aldehydes (entries 7, 10, 12 and 15). Selectivity drops significantly when ZnCl₂ and/or trimethylsilyl chloride are deleted from the reaction mixture (entries 6 and 11).



Scheme 1 Reagents: i, LiNPr₂; ii, Me₃SiCl; iii, ZnCl₂

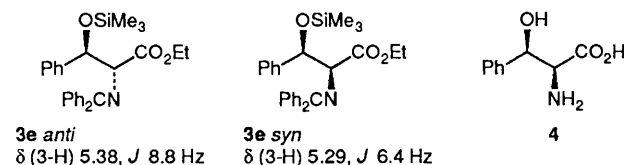


Table 1 Products from ZnCl₂ catalysed condensations of trimethylsilylketene acetals with aldehydes RCHO

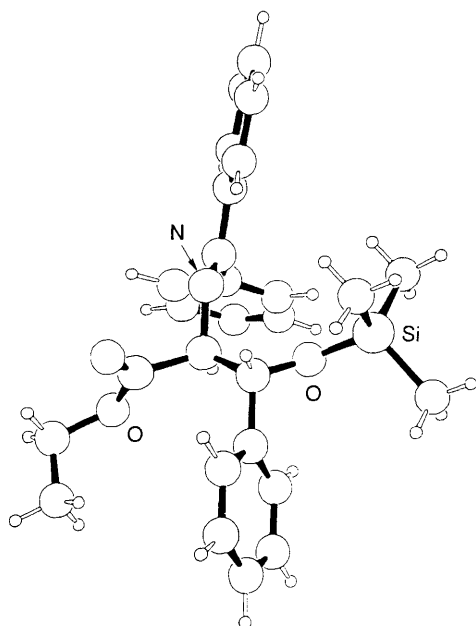
Entry	R	ZnCl ₂ ^a (%)	Yield ^b (%), product	<i>syn</i> : <i>anti</i> ^c
1	Et	5	90, 3a	58 : 42
2	Pr ⁱ	5	83, 3b	58 : 42
3	C ₆ H ₁₁	5	75, 3c	62 : 38
4	Bu ^t	5	67, 3d	92 : 8
5	Bu ^t	100	72, 3d	23 : 77
6	Ph	5	66, 3e	43 : 57 ^d
7	Ph	5	81, 3e	96 : 4
8	Ph	100	77, 3e	61 : 39
9	4-NO ₂ C ₆ H ₄	5	55, 3f	65 : 35
10	4-MeOC ₆ H ₄	5	90, 3g	100 : 0
11	2-Thienyl	0	66, 3h	55 : 45
12	2-Thienyl	5	84, 3h	89 : 11 ^e
13	2-Thienyl	100	40, 3h	28 : 72
14	2-Thienyl	300	53, 3h	41 : 59
15	2-Furyl	5	79, 3i	69 : 31

^a % based on **1**. ^b Yield of isolated material **3** after column chromatography. ^c Ratios determined by capillary GLPC except entry 9 for which ¹H NMR was used. ^d No Me₃SiCl used. ^e Exactly the same ratio was obtained using Et₂O as solvent. ^f Lowered yields due to nonhydrolytic work-up to avoid desilylation.

† *syn* and *anti* defined following ref. 8. The amino acid threonine is *syn* in this convention.

‡ The presence of unstable **2** in solution, presumably the thermodynamically determined isomer, was demonstrated by ¹H NMR spectroscopy.

§ Crystal data for *syn*-**3e**: C₂₇H₃₁NO₃Si, *M* = 445.64, triclinic, space group P $\bar{1}$, *a* = 9.449(1), *b* = 9.958(2), *c* = 15.297(4), Å, α = 84.59(2), β = 75.97(1), γ = 67.18(1)°, *V* = 1287.1 Å³, *Z* = 2, *D_c* = 1.150 g cm⁻³, Mo-K α radiation, 5961 reflections, 1° \leq θ \leq 27°, 3205 reflections had *I* > 3 σ (*I*) and were used in the data refinement. Enraf-Nonius CAD-4 diffractometer; structure determination at 293 K. Scaling factors, Lorentz and polarization corrections were applied to the data. The linear absorption coefficient is 1.12 cm⁻¹. No absorption corrections were made. The structure was partly solved by direct methods. The remaining atoms, including hydrogens, were revealed from succeeding Fourier syntheses. The final residuals were *R* = 0.069 and *R_w* = 0.076, based on 289 variables, maximum Δ / σ = 0.25, maximum and minimum peak heights in final difference map 0.58 and -0.56 e Å⁻³. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue no. 1.

Fig. 1 *syn-3e*

Equivalent (based on **1**) amounts of ZnCl_2 lead to moderate (entry 8) or profound (entries 5 and 13) reversal of the sense of stereoselection. We have observed a similar effect in certain cross-coupling reactions.⁹

syn-Selectivity is generally observed for non-cyclic transition states for the aldol condensation.¹⁰ This likely applies here also in the presence of catalytic quantities of ZnCl_2 . This is most probably present as Li_2ZnCl_4 ; the zincate anion aids in desilyating the ketene acetal **2**. A relatively hard enolate is generated which, however, is sensitive to electronic effects in the aldehyde acceptor (entries 9 and 10).¹¹ In the presence of

stoichiometric ZnCl_2 aldol condensation apparently proceeds at least in part through cyclic transition state with the thermodynamically most stable enolate. ZnCl_2 appears to be unique in its ability to steer stereoselectivities in different types of reactions.⁹

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