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

Anne W. van der Werf,[a] Richard M. Kellogg*[a] and F. van Bolhuis[b]

[a] *Department of Organic Chemistry, University of Groningen, Nijenborgh 16, 9747 AG Groningen, The Netherlands*
[b] *Crystal Structure Centre, Department of Chemistry, University of Groningen, Nijenborgh 16, 9747 AG Groningen, The Netherlands*

Schiff bases formed from condensation of glycine esters with diphenylmethyleneamine have been silylated followed by condensation with aliphatic and aromatic aldehydes at room temperature in the presence of catalytic amounts of $ZnCl_2$; 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 $ZnCl_2$.

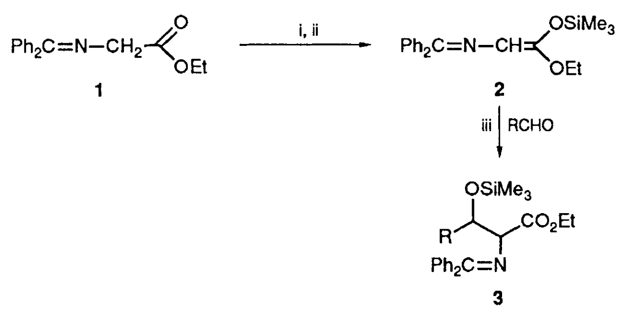
Because of the pharmacological and biological interest much effort has been expended the past twenty years in stereoselective syntheses of α-amino-β-hydroxy acids.[1] Glycine esters have often served as starting materials. For example, *N*-pyruvylideneglycinato-copper(II) complexes,[2] *N,N*-bis-(trimethylsilyl)glycine 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.

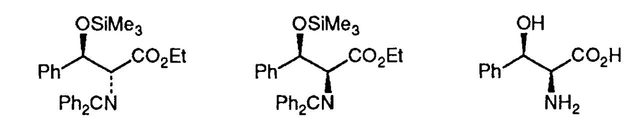
The condensation of **2**, prepared by deprotonation of **1** with lithium diisopropylamide followed by quenching with excess of trimethylsilyl chloride,‡ with various aldehydes takes place in tetrahydrofuran (THF) solution containing $ZnCl_2$ (5% based on **1**) at room temperature (12 h). The products 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 $ZnCl_2$ and/or trimethylsilyl chloride are deleted from the reaction mixture (entries 6 and 11).



Scheme 1 *Reagents*: i, $LiNPr^i_2$; ii, Me_3SiCl; iii, $ZnCl_2$



3e *anti* δ (3-H) 5.38, *J* 8.8 Hz
3e *syn* δ (3-H) 5.29, *J* 6.4 Hz
4

Table 1 Products from $ZnCl_2$ catalysed condensations of trimethylsilylketene acetals with aldehydes RCHO

Entry	R	$ZnCl_2$[a] (%)	Yield[b] (%), product	*syn* : *anti*[c]
1	Et	5	90, **3a**	58 : 42
2	Pr^i	5	83, **3b**	58 : 42
3	C_6H_{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-$NO_2C_6H_4$	5	55, **3f**	65 : 35
10	4-$MeOC_6H_4$	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,[f] **3h**	28 : 72
14	2-Thienyl	300	53,[f] **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 Me_3SiCl used. [e] Exactly the same ratio was obtained using Et_2O 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**: $C_{27}H_{31}NO_3Si$, 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 Å^3, Z = 2, D_c = 1.150 g cm^{-3}, Mo-Kα radiation, 5961 reflections, 1° ≤ θ ≤ 27°, 3205 reflections had $I > 3\sigma(I)$ 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.

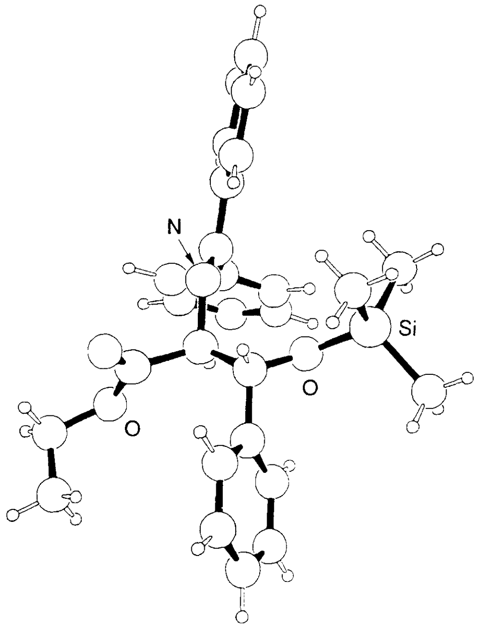


Fig. 1 *syn*-**3e**

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]

This research was supported in part by the Dutch Science Foundation (ZWO) administered through the Office for Chemical Research (SON).

Received, 27th December 1990; Com. 0/05808D

References

1 H. Giepel, J. Gloede, K. P. Hilgetag and H. Gross, *Chem. Ber.*, 1964, **98**, 1677; T. Nakatsuka, T. Miwa and T. Mukaiyama, *Chem. Lett.*, 1981, 279; S. Saito, N. Bunya, M. Inaba, T. Moriwake and S. Torii, *Tetrahedron Lett.*, 1985, **26**, 5309; D. A. Evans, E. B. Sjogren, A. E. Weber and R. E. Conn, *Tetrahedron Lett.*, 1987, **28**, 39; J. F. Dellaria and B. D. Santarsiero, *Tetrahedron Lett.*, 1988, **29**, 6079.

2 S. Ohdan, T. Ichikawa, Y. Araki and Y. Ishido, *Bull. Chem. Soc. Jpn.*, 1974, **47**, 1295.

3 A. Shanzer, L. Somekh and D. Butina, *J. Org. Chem.*, 1979, **44**, 3967.

4 T. Oesterle and G. Simchen, *Synthesis*, 1984, 403.

5 Y. N. Belokon', A. G. Bulychev, S. V. Vitt, V. T. Struchkov, A. S. Batsanov, T. V. Timofeeva, V. A. Tsyryapkin, M. G. Ryzhov, L. A. Lysova, V. I. Bakhmutov and V. M. Belikov, *J. Am. Chem. Soc.*, 1985, **107**, 4252.

6 H. Kuzuhara, N. Watanabe and M. Ando, *J. Chem. Soc., Chem. Commun.*, 1987, 95.

7 G. Guanti, L. Banfi, E. Narisano and C. Scolastico, *Tetrahedron*, 1988, **44**, 3761.

8 C. H. Heathcock, C. T. Buse, W. A. Kleshik, M. C. Pirrung, J. E. Sohn and J. Lampe, *J. Org. Chem.*, 1980, **45**, 1066.

9 G. C. Cross, B. K. Vriesema, G. Boven, R. M. Kellogg and F. van Bolhuis, *J. Organomet. Chem.*, 1989, **370**, 3570.

10 E. Nakamura, S. Yamago, D. Machi and J. Kuwajima, *Tetrahedron Lett.*, 1988, **29**, 2207.

11 R. Noyori, I. Nishida and I. Sakata, *J. Am. Chem. Soc.*, 1981, **103**, 2106.