Pergamon

Tetrahedron: *Asymmetry* 10 (1999) 1617–1622

TETRAHEDRON: *ASYMMETRY*

Diastereoselective addition of HCN to Garner's aldehyde

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Received 22 April 1999; accepted 26 April 1999

Abstract

The hydrocyanation of *N*-Boc-*N*,*O*-isopropylidene-L-serinal **1** (Garner's aldehyde) is described. The influence of various reaction conditions (solvent, temperature, addition of a Lewis acid, presence of a biocatalyst) on the stereochemical outcome of the addition of HCN was investigated. The use of 2-pentanol as the solvent at room temperature afforded complete stereoselectivity. X-Ray analysis of the product showed the *anti* configuration. The results can be readily explained on the basis of a Felkin–Anh type model. © 1999 Elsevier Science Ltd. All rights reserved.

1. Introduction

Recently, a number of articles have appeared describing the stereoselective addition of nucleophiles[1a–d,2] to *N*-Boc-*N*,*O*-isopropylidene-L-serinal **1** (Garner's aldehyde). These included Grignard reagents,[1a] the lithium derivative of a propargyl ether[2] and a Wittig olefination.[3] We hereby want to report the stereoselective addition of hydrogen cyanide to Garner's aldehyde producing its α-hydroxynitrile (cyanohydrin).

The synthesis and application of chiral cyanohydrins is a major interest in our group. In recent years a simple system has been developed by which these cyanohydrins can be prepared in excellent enantiomeric purity by the asymmetric addition of HCN to aldehydes in a reaction catalyzed by the enzyme *R*-oxynitrilase, as present in almond meal (E.C. 4.1.2.10).[4] The cyanohydrins thus obtained are known to possess the *R*-configuration[5] and have been shown to be versatile chiral building blocks in organic synthesis. Further modification can produce a broad range of enantio- and diastereomerically pure compounds, including β-hydroxy-α-amino acids,[6] β-hydroxy-nitrones,[7] α-hydroxy-β-amino acids,[8] and β-γ-unsaturated-α-hydroxy esters.[9]

A wide variety of substrates can be employed in the *R*-oxynitrilase catalyzed reaction. These include aromatic, heterocyclic, and saturated as well as α,β-unsaturated and ω-unsaturated aliphatic

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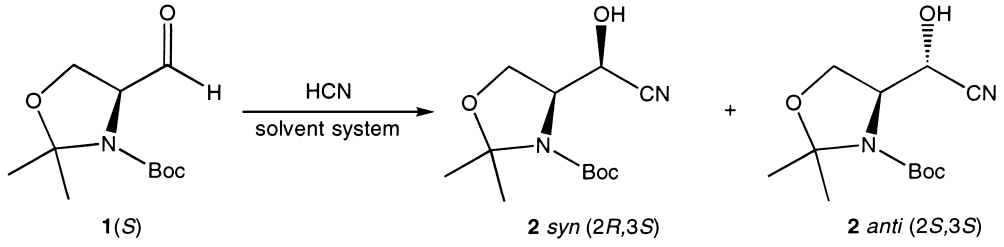
PII: S0957-4166(99)00159-7

aldehydes.[10a–c] In one case where the influence of α-substitution on the enzymatic reaction was investigated, a substantial decrease in selectivity was found.[11a–b] We therefore first investigated whether Garner's aldehyde is a suitable substrate for *R*-oxynitrilase.

The reaction is depicted in Scheme 1. Garner's aldehyde **1** reacts with HCN to produce the 2*R*,3*S* (*syn*) and the 2*S*,3*S* (*anti*) diastereoisomers of 3-(*N*-*tert*-butoxycarbonyl)amino-2,4-dihydroxy-3,4-*N*,*O*-isopropylidenebutanenitrile **2**.



1(*S*) **2** *syn* (2*R*,3*S*) **2** *anti* (2*S*,3*S*)

Scheme 1. Addition of HCN to Garner's aldehyde **1**

2. Results and discussion

When the hydrocyanation of Garner's aldehyde was catalyzed by the enzyme *R*-oxynitrilase, a preponderance of the *syn* diastereoisomer was expected to be formed. Stirring serinal **1** with 2 equivalents of HCN in the presence of almond meal[4] in an aqueous buffer system (pH 5.4) at 5°C gave a mixture of diastereoisomers in a ratio of 10:90. When the reaction was performed at room temperature without the enzyme, a similar ratio was found. It was therefore concluded that Garner's aldehyde was not a good substrate for *R*-oxynitrilase.

In order to investigate further the diastereoselectivity of the addition, a number of different reaction conditions were applied. The results are presented in Table 1. The diastereomeric excesses shown in this table were determined by GC after *tert*-butyldiphenylsilyl protection of the hydroxyl group. Silyl protection of cyanohydrins under controlled conditions is known to proceed without significant loss of enantiomeric purity.[12]

The use of a polar aprotic solvent, such as ethyl acetate (entry **d**), or less polar aprotic solvents, such as toluene (entry **h**) and diisopropyl ether (entry **c**), gave rise to low diastereoselectivity.

Lewis acids are known to accelerate addition reactions to aldehydes and also to increase the diastereoselectivity in certain cases. The addition of zinc chloride (entry **e**), boron trifluoride (entry **f**) or titanium (IV) isopropoxide (entry **g**) to the reaction mixture, did lead to an increase in diastereoselectivity but did not result in the exclusive formation of one diastereoisomer.

By performing the reaction at lower temperatures the diastereoselectivity of the HCN addition could be improved, as indicated by a comparison of entries **h** and **i**. In this way, a 8:92 ratio could be obtained.

The use of 2-pentanol, a polar protic solvent, led to the exclusive formation of only one diastereoisomer. The reaction proceeded in quantitative yield and took 4.5 h to reach completion. A higher alcohol was used as the solvent because it was known that cyanohydrins only show a limited stability in methanol, ethanol and 2-propanol. With higher alcohols no decomposition was observed at room temperature.[13]

Clearly the best results were obtained with 2-pentanol as the solvent. The exclusively formed cyanohydrin was obtained as a solid. After recrystallization from hexane and dichloromethane a suitable colorless crystal was obtained for X-ray analysis. Fig. 1 shows an ORTEP projection of the X-ray structure, together with the structural formula, suggesting the existence of a hydrogen bond between

Table 1
Diastereoselectivity of the hydrocyanation of Garner's aldehyde

Entry	Solvent System	Temp. (°C)	reaction time	*syn*:*anti* ratio[1]	d.e. [1](%)
a	diisopropyl ether, R-oxynitrilase, aq. buffer pH 5.4	5	2 w	10 : 90	80
b	diisopropyl ether	5	3 d	26 : 74	48
c	diisopropyl ether, aq. buffer pH 5.4	RT	12 h	18 : 82	64
d	ethyl acetate	RT	12 h	49 : 51	2
e	ethyl acetate, $ZnCl_2$	RT	12 h	39 : 61	22
f	ethyl acetate, $BF_3 \cdot OEt_2$	RT	12 h	8 : 92	84
g	ethyl acetate, $Ti(O\text{-}i\text{-}Pr)_4$	RT	12 h	35 : 65	30
h	toluene	RT	1 w	34 : 66	32
i	toluene	-78→RT	1 w	8 : 92	84
j	2-pentanol	RT	4.5 h	≤ 0.5 : ≥ 99.5	≥ 99

[1] Determined with GC after TBDPS protection of the crude cyanohydrin reaction mixture.

the hydroxyl group and the oxygen atom of the oxazolidine ring. A Newman projection along the C_2/C_3 axis is also depicted. X-Ray analysis clearly shows that the cyanohydrin possesses the *anti* configuration.

A model was devised for the transition state of the addition of HCN to Garner's aldehyde in order to explain the preference for the formation of the *anti* diastereoisomer (Fig. 2). Two models for the prediction of the stereochemical outcome of addition to a carbonyl group are known from literature. In the Cram model,[14] a chelation-controlled transition state leads to the *syn* adduct. In the Felkin–Anh model,[15a–b] a transition state controlled by steric hindrance leads to the *anti* adduct. Our results can be best explained by the latter model. The strong solvent effect that is observed supposedly results from hydrogen bonding in the transition-state, as depicted in Fig. 2.

Due to hydrogen bonding between the oxygen of the aldehyde, the oxygen of the oxazolidine ring and the proton of a polar protic solvent, a particularly stable chair-like transition state can be formed. Steric hindrance of the now strongly solvated *N*-Boc group and the two methyl substituents of the isopropylidene group then causes the cyanide ion to attack exclusively from the *Re* side. The cyanohydrin formed retains the chair-like conformation through an intramolecular hydrogen bond between the hydroxyl group of the cyanohydrin and the oxygen atom from the oxazolidine ring.

The presence of hydrogen bonding in **2** *anti*, was confirmed by IR spectroscopy, which showed a hydrogen bonded OH at 3334 cm^{-1}. Also the position of the oxygen atoms in the ORTEP projection (Fig. 1) indicated the presence of an intramolecular hydrogen bond.

The obtained cyanohydrin is a new and potentially versatile chiral building block. The presence of the

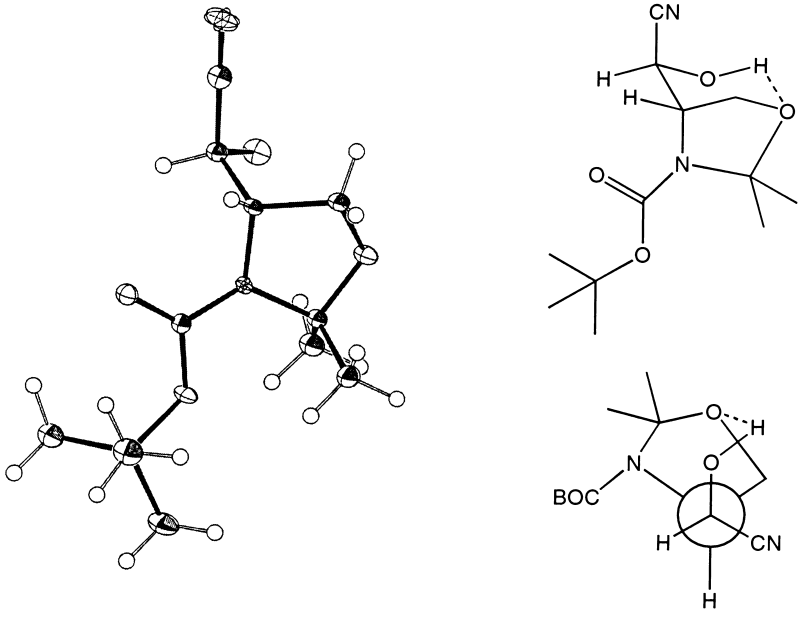


Figure 1. Different projections of (2*S*,3*S*)-3-(*N*-*tert*-butoxycarbonyl)amino-2,4-dihydroxy-3,4-*N*,*O*-isopropylidenebutanenitrile. In the ORTEP drawing not all atoms of the *t*-butyl group are clearly visible

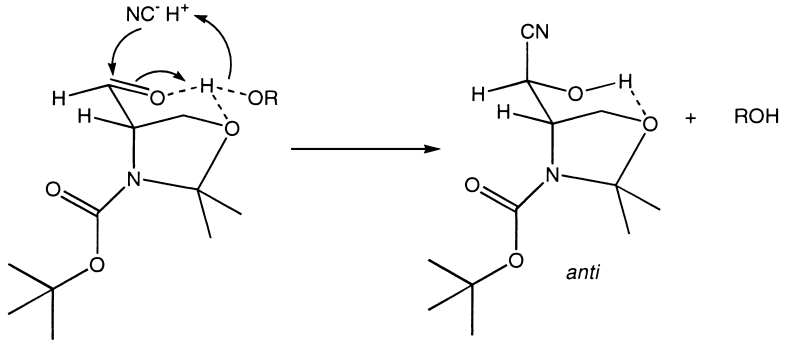


Figure 2. Proposed model for the hydrocyanation of Garner's aldehyde. ROH represents a polar protic solvent

introduced nitrile moiety opens up a range of possible synthetic transformations. The cyanohydrin could for example be transformed into a sphingosine.[16a–c] Further syntheses with this cyanohydrin are under current investigation.

3. Conclusions

Hydrocyanation of Garner's aldehyde at room temperature using 2-pentanol as the solvent, affords the corresponding *anti* cyanohydrin in a quantitative yield and with a de of ≥99%.

4. Experimental

4.1. General methods and materials

^{1}H and ^{13}C NMR spectra were recorded on a Bruker DMX-600 instrument. Samples were measured in $CDCl_3$, with Me_4Si as an internal standard for ^{1}H NMR, and $CDCl_3$ as an internal standard for ^{13}C NMR; δ in ppm, J in hertz. Diastereomeric ratios were determined by GC (column: CP-SIL-88, WCOT fused silica, 50 m×0.25 mm, oven temperature: 140°C, detection temperature: 250°C, injection temperature: 250°C). After TBDPS protection of the cyanohydrin; diastereomer I: rt 27.6 min, diastereomer II: rt 28.5 min. Melting points were measured on a Büchi melting point apparatus and are uncorrected. Optical rotations were measured using a Propol automatic polarimeter. Elemental analyses were performed on a Perkin–Elmer 2400 analyzer. Infrared spectra were obtained on a Perkin–Elmer FT-IR spectrometer Paragon 1000, Golden Gate Diamond ATR. Ethyl acetate was distilled prior to use. Garner's aldehyde **1** was prepared according to the literature.[17a–d]

4.2. General procedure for the hydrocyanation reaction

In an Erlenmeyer flask 0.44 g (9 mmol) of NaCN was dissolved in 10 ml of cold water. The pH of this solution was adjusted to 5.5 by addition of citric acid: Caution: formation of toxic hydrogen cyanide! The resulting hydrogen cyanide solution was extracted with the solvent of choice (3×4 ml). This solution was added to 0.92 g (4 mmol) of Garner's aldehyde **1**. The mixture was stirred. Reaction times are shown in Table 1. The mixture was poured into water and extracted with the solvent (3×10 ml). The combined organic layers were washed with water (5 ml) and saturated brine (5 ml), dried ($MgSO_4$) and concentrated in vacuo.

4.3. Enzyme catalyzed reaction (entry ***a***)

See Marcus et al.[18]

4.4. Lewis acid catalyzed reactions (entries ***e***, ***f*** and ***g***)

Equimolar addition of $ZnCl_2$ and Ti(*O*-*i*Pr)$_4$ and catalytic addition of $BF_3 \cdot OEt_2$.

4.5. *(2*S*,3*S*)-3-(*N-tert-*Butoxycarbonyl)amino-2,4-dihydroxy-3,4-*N,O-*isopropylidenebutanenitrile*

Melting point: 97°C. $[\alpha]_D^{20}$ −3.1 (c=0.05, $CHCl_3$). ^{1}H NMR: δ=1.53 (s, 9H, Me_3C), 1.67 (s, 6H, Me_2C), 3.80–3.86 (dd, 1H, CH_2CHN, J_{ab}=3.7 Hz, J_{ax}=8.8 Hz), 4.15–4.23 (ABX-system, 2H, CH_2CHN), 4.51–4.56 (d, 1H, CHOH, J=9.5 Hz, after D_2O-shake: s), 6.32–6.37 (d, 1H, OH, exchanged with D_2O). ^{13}C NMR: δ=24.6, 25.9 (Me_2C), 28.1 (Me_3C), 61.2 (CHN), 64.7 (CH_2O), 65.4 (CHOH), 82.9 (Me_3C), 95.6 (Me_2C), 117.8 (C≡N), 153.4 (C=O). IR (pure): 3334, 2361, 1660 cm^{-1}. $C_{12}H_{20}N_2O_4$ (256.30): calcd C 56.24, H 7.86, N 10.93; found C 56.63 H 7.87, N 11.04.

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