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REVERSAL OF ASYMMETRIC INDUCTION IN STEREOSELECTIVE STRECKER SYNTHESIS ON GALACTOSYL AMINE AS THE CHIRAL MATRIX

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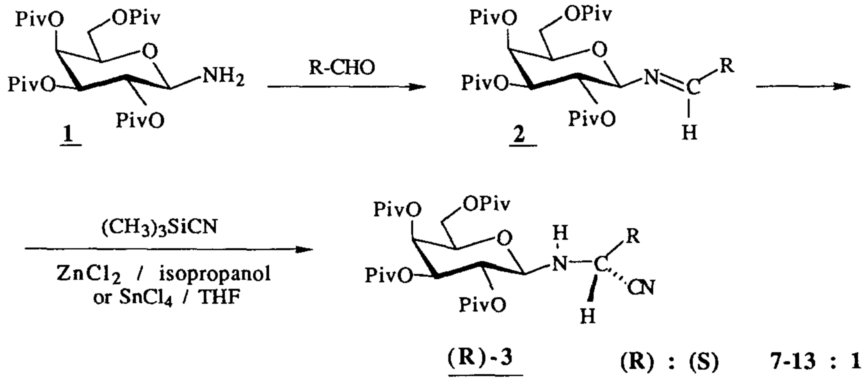
Summary: The reversal of the direction of asymmetric induction in Lewis acid catalyzed Strecker synthesis using the 2,3,4,6-tetra-O-pivaloyl-β-D-galactopyranosyl amine **1** is described. In isopropanol or tetrahydrofuran **1** had given (R)-diastereomers of the corresponding α-amino nitriles preferably. However, in chloroform in the presence of heterogeneous zinc chloride the same auxiliary alternatively leads to an excess of the (S)-diastereomers.

The α-amino acids constitute an important class of natural chiral compounds. Consequently, their diastereoselective synthesis is receiving attention since a long time¹⁾. Among the methods applied, the Strecker synthesis has the advantage that the α-amino nitriles are accessible from inexpensive starting materials in high yields and without application of organometallic reagents. Chiral auxiliaries, successfully used in these reactions, are α-phenylethylamine¹⁻⁶⁾ and (4S,5S)-5-amino-2,2-dimethyl-4-phenyl-1,3-dioxane⁷⁽⁸⁾.

Recently we found an effective diastereoselective Strecker synthesis of N-glycosyl-(R)-α-amino nitriles **(R)-3** using the 2,3,4,6-tetra-O-pivaloyl-β-D-galactopyranosyl amine **1** as the chiral matrix⁹⁾.

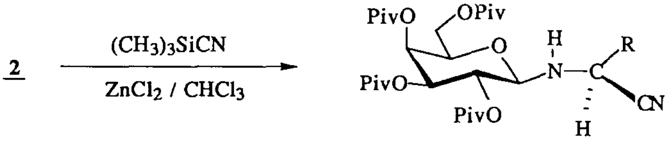


(R) : (S) 7-13 : 1

(eq. 1)

For this purpose the Schiff bases 2 formed from the galactosylamine 1 and aldehydes were allowed to react with trimethylsilyl cyanide in the presence of zinc chloride in isopropanol or tin tetrachloride in tetrahydrofuran. After one recrystallization from heptane or dichloromethane/heptane the pure (R)-amino nitriles (R)-3 were obtained in yields of 75-90%$^{9)}$. The galactosyl amine 1 proved to be also efficient in a diastereoselective Ugi synthesis of (R)-amino acid derivatives$^{10)}$.

We recently found that the direction of asymmetric induction in the Strecker synthesis using the galactosyl amine 1 as the chiral auxiliary surprisingly can be reversed by changing the solvent. In chloroform in the presence of solid zinc chloride the N-galactosyl aldimines 2 react with the trimethylsilyl cyanide to give alternatively the (S)-diastereomers of the amino nitriles (S)-3 in excess.



(S)-3 (S) : (R) 3-9 : 1

(eq. 2)

Table1: Diastereoselective Strecker Synthesis of (S)-α-Amino Nitriles (S)-3 Using the Galactopyranosyl Amine 1 as the Chiral Template (eq. 2)

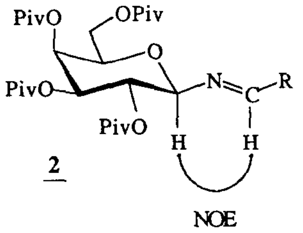
	R 3	$ZnCl_2$ [mol-%]	temperature [°C]	reaction time	diastereoselectivity$^{a)}$ (R) : (S) 3	100.6 MHz-^{13}C-n.m.r δ [ppm] (R) / (S) 3	α-anomer$^{a)}$ of 3 [%]
a	$(CH_3)_3C$-	5	20	2 h	1 : 9	CN: 119.6 / 118.7 C-1: 90.2 / 82.4	10
b	$(CH_3)_2CH$-	100	20	1 h	1 : 5	CN: 119.4 / 118.0 C-1: 89.2 / 87.1	traces
c	C_6H_5-CH_2-CH_2-	100	20	15 min	1 : 3	CN: 120.2 / 119.1 C-1: 88.8 / 87.0	10
d	p-CH_3-C_6H_4-	100	0	1 h	1 : 4.5	CN: 119.3 / 118.5	traces
e	p-F-C_6H_4-	100	20	15 min	1 : 3	CN: 118.9 / 118.2	5
f	p-Cl-C_6H_4-	5	20	7 h	1 : 4	C-1: 87.1 / 86.9	traces
	"	300	20	1 h	1 : 5		no
g	m-Cl-C_6H_4-	5	0	10 h	1 : 6	C-1: 87.3 / 86.4	5
	"	100	20	15 min	1 : 5		10

a) Detected by HPLC

At room temperature or at 0°C (see table 1) these reactions give almost quantitative yields (>90%). The ratios of diastereomers 3 were detected directly from the hydrolyzed reaction mixtures by means of both analytical HPLC (diode-array detection) and 400 MHz ^{1}H-n.m.r. spectroscopy. Both methods gave corresponding results (see table 1). It should be noted that in the absence of zinc chloride the reaction does not occur. However, by using dry hydrogen cyanide instead of trimethylsilyl cyanide in chloroform, the (S)-diastereomers (S)-3) are also formed preferably. This was also found for a slow reaction in the absence of the zinc catalyst. Other lewis acid catalysts tested so far (titanium tetrachloride, aluminium trichloride, boron trifluoride etherate, magnesium chloride) are less effective in both diastereoselectivity and chemical yield.

The results quoted in table 1 show that the ratios of diastereomers achieved in these reversed stereoselections (eq. 2) are somewhat lower than those obtained in the (R)-selective reactions (eq. 1) in homogeneous polar media9). Prolonged reaction times seem to favour the formation of α-anomers as the by-products. It is an important fact for the utilization of the method that the minor components (R)-3 can be crystallized and, thus, separated almost quantitatively from the diastereomeric mixture (R)-3 / (S)-3. From the remaining mixtures enriched in (S)-diastereomers (ratio ca. 20 : 1), pure (S)-diastereomers of the α-amino nitriles (S)-3 are obtained in yields of 50-75% after chromatography. The (S)-tertiary-leucine derivative11) (S)-3a is isolated in pure form by recrystallization from heptane.

We conclude that by the use of the O-pivaloyl protected galactosylamine as the template in Strecker syntheses both diastereomeric series of the N-glycosyl-α-amino nitriles 3 can be obtained selectively and alternatively. These reactions (eq. 1 and eq. 2) constitute a rare case in which both alternative stereoselections are achieved using the same chiral auxiliary12). Furthermore, the aldimines 2 used as the starting materials in both stereoselections have identical configuration (E-isomers) as can be demonstrated by 400 MHz ^{1}H-n.m.r. spectroscopy. Also the preferred conformation seems to be identical in THF-[d_8] and in $CDCl_3$.



2

A

Due to a charge transfer from the C=N-π-orbital to the σ*-orbital of the ring-C-O-bond, conformation A is preferred. This can be shown by a strong NOE between the aldimine proton and the anomeric proton.

The reversal of the stereoselection described here may be caused by differing complexation of the zinc chloride catalyst and altered presentation of the nucleophilic cyanide in the different media. In the polar solvent isopropanol free cyanide which preferably gives the (R)-diastereomers R-3 is present, whereas in chloroform the nucleophilicity of the cyanide obviously has to be liberated by an interaction of the silyl derivative with a ligand of the zinc catalyst. We note, however, that the direction of asymmetric induction in the Ugi reaction using **1** as the template[10] cannot be reversed by changing the solvent.

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11) (S)-3a: m.p. 139 °C; $[\alpha]_D^{22}$=-1.02° (c=1, $CHCl_3$); 100.6 MHz-^{13}C-n.m.r ($CDCl_3$): δ [ppm] 118.7 (CN); 82.4 (C-1); 56.9 (α-CH); 39.08, 38.85, 38.75 ($C(CH_3)_3$; Piv); 34.1 ($C(CH_3)_3$; t-Leu).
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b) More often, inversion of asymmetric induction has been observed by application of different electrophilic catalysts, for instance, in the reduction of ketons with sodium borohydride: A. Hirao, S. Itsuno, M. Owa, S. Nagami, H. Mochizuki, H. H. A. Zoorov, S. Niakahama, N. Yamazaki; J. Chem. Soc. Perkin Trans. I **1981**, 900; and
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