Tetrahedron Letters, Vol.31, No.26, pp 3797-3800, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

STEREOSELECTIVE ADDITION OF FURYLLITHIUM TO VARIOUSLY *N,N*-DIPROTECTED D-ALANINALS

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Abstract: A highly stereoselective route to derivatives of 2-amino-1-(2'-furyl)-propan-1-ol *via* addition of furyllithium to variously *N,N*-diprotected D-alaninals is described. An efficient conversion of these compounds into aminosugar precursors - chiral uloses is also presented.

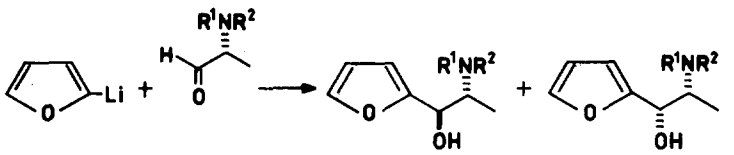
During our studies directed towards the synthesis of polyhydroxylated open-chain compounds,[1] we have observed high *anti*-diastereoselectivity in the reaction of 2,3-*O*-isopropylidene-D-glyceraldehyde with 2-methylfuryllithium, carried out in the presence of zinc bromide. High-pressure reactions of the same aldehyde with 2-methyl-[2] or 2,5-dimethylfuran[3] exhibited also relatively high *anti*-diastereoselectivity. On the other hand, we have recently demonstrated a high degree of asymmetric induction in the [4+2] cycloaddition reaction of activated 1,3-dienes with *N,N*-diprotected D-alaninals under high[4] as well as under ambient pressure.[5] These results prompted us to study the addition reaction of furyllithium with *N*-protected α-amino aldehydes.

We decided to use in this study derivatives of D-alaninal since it represents the simplest example of chiral α-amino aldehydes. However, *N*-monoprotected D-alaninals were unstable towards furyllithium. This fact called for the use of *N,N*-diprotected alaninals **1**.

Compounds **2** and **3**, products of addition of furyllithium to D-alaninals **1** (Scheme 1), are readily oxidized[6] into corresponding 2,6-dihydropyran-3-one derivatives of type **4** and **5** (Scheme 2), which provide an excellent template for the efficient and highly stereoselective introduction of a variety of functional groups and substituents.[7] This method opens an access to the synthesis of many higher aminosugars in optically pure form.[8]

Recently Reetz *et al.* have demonstrated high stereoselectivity in additions of a variety of metalloorganic reagents,[9] trimethylsilylcyanide[10] and lithiated heterocycles[11] to *N,N*-dibenzyl α-amino aldehydes. Unfortunately, *N,N*-dibenzyl protecting group used by Reetz is unstable under oxidative conditions applied for transformation of carbinols **2** and **3** into 2,6-dihydropyran-3-ones **4** and **5**.[6] We overcame this difficulty by applying of Me-Boc, Bn-Boc and Bn-Ts protecting groups. In this manner *N,N*-diprotected D-alaninals **1** easily reacted with furyllithium affording the adducts **2** and **3** with high

anti-stereoselectivity in very good yields[12] (Scheme 1).

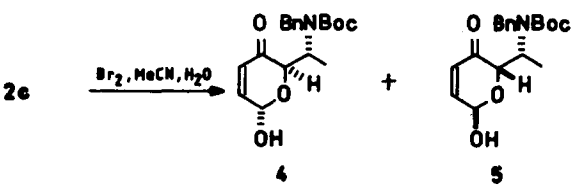


1a	$R^1=R^2=Bn$	**2a**	91 : 9	**3a**
1b	$R^1=Me, R^2=Boc$	**2b**	96 : 4	**3b**
1c	$R^1=Bn, R^2=Boc$	**2c**	90 :10	**3c**
1d	$R^1=Bn, R^2=Ts$	**2d**	92 : 8	**3d**

Scheme 1

In all cases *anti*-stereoselectivity was observed as evidence of nonchelation control of the reaction.[13] Addition of a strong chelating Lewis acids such as $TiCl_4$ did not reverse direction of asymmetric induction. Apart from compounds **2a** and **3a**, which were readily separable by column chromatography, diastereoisomeric ratio was determined by ^1H NMR (500 MHz). Rotation around Boc - nitrogen atom bond in compounds **2b**, **3b** and **2c**, **3c** is strongly retarded. It is revealed by broadening of all signals in the ^1H NMR spectrum and by decay of multiplicity. In these cases diastereomeric ratio was determined after conversion of mixtures **2b**, **3b** and **2c**, **3c** into corresponding oxazolidinones by treatment with CF_3COOH in CH_2Cl_2 at room temperature. The configurational assignments for compounds **2b** and **2c** were based on analysis of the vicinal protons coupling constants in ^1H NMR spectrum of their oxazolidinones.[14] Stereochemical assignments for other compounds **2** and **3** were attributed on the basis of ^1H NMR analysis carried out for original adducts and by analogy with results of chemical correlation published by Reetz *et al.*[9,11]

Apart from the *N,N*-dibenzyl derivatives (**2a** and **3a**), all amino alcohols obtained were efficiently transformed into corresponding aminosugar precursors-uloses of type **4** and **5**, under effect of bromine in an acetonitrile-water solution[6,15] (Scheme 2).



Scheme 2

The mixture of uloses **4** and **5** bearing Bn and Boc protecting groups on the nitrogen atom was crystalline. Therefore, the final proof of the structure and stereochemistry of compound **4** was established by single-crystal X-ray analysis[16] (Fig. 1).

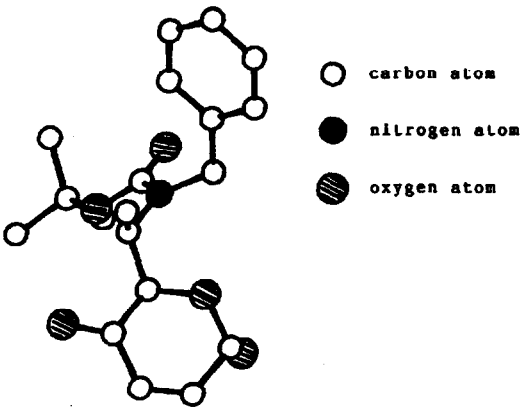


Fig. 1. Computer generating perspective drawing of compound **4**

X-ray crystallography enabled the stereochemistry to be assigned as *anti* in line with the previous attribution. Additionally, disorder of the ulose ring was observed, arising from the existence of a major diastereoisomer as α- and of a minor one as β-anomer exclusively.[17]

Further studies leading to application of this methodology to the synthesis of naturally occurring aminosugars are in progress.

Acknowledgment: This work was supported by the Polish Academy of Sciences (Grant CPBP 01.13), and by the Ministry of National Education (Grant RP.II.10).

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(12) Typical procedure: To a solution of furane (4 mmol) in dry THF (5 ml) was added 3 mmol of BuLi at -40°C. A reaction mixture was warmed to room temperature for 3h. The mixture was then cooled to -78°C and solution of compound 1 (1 mmol) in 2 ml of THF was added. After 3h stirring at -78°C, the reaction mixture was hydrolized with 5 ml of a saturated NH_4Cl solution. The aqueous layer was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and after evaporation of solvents, the residue was purified by flash chromatography. In all cases the yield of a mixture of products 2 and 3 was in the range of 80-90% . All products were fully characterized by their combustion analysis and their spectral data.

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(14) For oxazolidinone derived from compound **2b** the vicinal coupling constant was 7.9 Hz, and for that derived from 2c it was 7.5 Hz. This is in good agreement with the literature data.[11,18]

(15) Typical procedure: To a vigorously stirred and cooled (-5°C) solution of compounds 2 and 3 (1 mmol) in a mixture of MeCN-H_2O (9:1 v/v, 5 ml) bromine (1.3 mmol) was added and stirring was continued for additional 10 min. Solid $NaHCO_3$ was added and the mixture was poured into Et_2O and washed with brine. After drying ($MgSO_4$) and evaporation of solvents the crude product was purified by flash chromatography. In all cases yields were in the range of 70-85 %. All products were fully characterised by their combustion analysis and their spectral data.

(16) Crystal data for compound **4**: $C_{19}H_{25}NO_5$, M_r = 347.41, monoclinic, space group $P2_1/c$, Z = 4, a = 9.490(2), b = 21.516(3), c = 10.279(2) Å, β = 115.31(1)°, V = 1897.3(3) Å^3, F(000) = 744, D_c = 1.22 Mg m^{-3}, μ(CuKα) = 0.68 mm^{-1}. The structure was solved by direct methods using the SHELXS-86 program and refined by full-matrix least-squares programs of the SHELXS-76, the final R value was 0.0573 (unit weights). The details of the crystal structure will be given in a separate paper.[17]

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(Received in UK 26 April 1990)