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Diastereoselective synthesis of 3-amino-1,2-diols by reductive alkylation of 2,3-dialkoxynitriles

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Abstract

The addition of Grignard reagents to acetonide protected *syn* 2,3-dihydroxynitriles, followed by reduction of the resulting magnesioimines, affords all *syn* 1,3-disubstituted 3-amino-1,2-diols in high enantiomeric purities.

Keywords: aminoalcohols; cyanohydrins; Grignard reagents; diastereoselection.

The stereocontrolled synthesis of aminoalcohols and aminodiols have attracted much interest in recent years because these core units are implicated in the synthesis of various biologically active molecules such as proteases inhibitors,[1] glycosphingolipides[2] or polyhydroxylated nitrogen heterocycles.[3]

These may be prepared by opening of an epoxyalcohol with a nitrogen nucleophile,[4] a reaction which regioselectivity is sometimes difficult to control, or by the stereocontrolled addition of organometallic reagents to imines and related compounds derived from protected polyhydroxylated aldehydes.[5]

We wish to report here a method which allows the stereoselective synthesis of all *syn* 1,3-disubstituted 3-amino-1,2-diols in high enantiomeric purity by reductive alkylation of *syn* 2,3-dialkoxynitriles.

In contrast with simple aliphatic nitriles, which are partially deprotonated in the α position by Grignard reagents, the α-alkoxy nitriles give the addition only, a reaction which allows the synthesis of α-alkoxy ketones after acidic hydrolysis. Starting from α-silyloxy nitriles, the reduction of the intermediate imines by sodium borohydride allowed the access to *anti* 1,2-aminoalcohols in good diastereoselectivity.[6] Very recently, the sequential addition of Grignard and organocerium reagents to dialkoxynitriles was applied to the synthesis of α,α-disubstituted α-amino acids.[7]

We thought that by using the acetonide protected *syn* 2,3-dihydroxynitriles **1**, the synthesis of which we have recently described,[8] it would be possible to stereoselectively synthesize protected aminodiols such as **2** or **3** (Scheme 1).[9]

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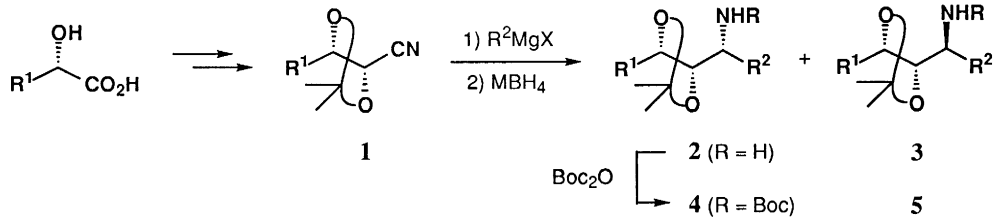


Scheme 1.

However, due to the presence of two oxygen atoms, it was difficult to predict a priori the stereoselectivity of this reaction. Indeed it is well known that the stereoselectivity of the addition of organometallic compounds to diprotected derivatives of glyceraldehyde,[10] or to the corresponding imines,[5] is highly dependent on the protecting groups.

First attempts were achieved with the unsubstituted nitrile **1a** which was prepared in nearly quantitative yield from the corresponding ester by transformation into primary amide (NH_3–EtOH, 25°C, 2 days) followed by dehydration with cyanuric chloride.[11] The condensation of *n*-BuMgBr in ether, followed by $NaBH_4$ reduction of the resulting imine, afforded the corresponding amine as a 30:70 mixture of *syn* and *anti* diastereomers (Table 1). After transformation into the *N*-Boc compounds **4aA** and **5aA**, the stereochemistry of the major diastereomer was determined by GC, according to the results previously observed during the reductive amination of the corresponding ketones.[12] We were unable to increase this diastereomeric ratio regardless of the reducing agent we used (L-selectride, Red-Al®, $LiAlH_4$, BH_3–THF). Moreover, when using zinc borohydride, we observed an inversion of stereochemistry leading to compounds **2aA** and **3aA** with a 60:40 ratio.

Table 1
Reductive alkylation of nitriles **1**

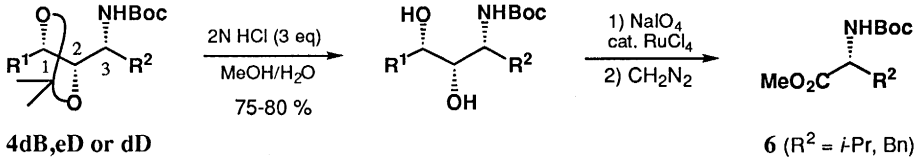
Nitriles **1**	R^1	R^2MgX	Reducing Agent	**2/3** (2,3-*syn*/2,3-*anti*)		**4 + 5** Yield %
1a	H	*n*-Bu (**A**)	$NaBH_4$	**aA**	30/70	-
1a	H	*n*-Bu	$Zn(BH_4)_2$	**aA**	60/40	-
1b	*i*-Pr	Bn (**B**)	$NaBH_4$	**bB**	83/17	78
1c	*i*-Bu	*c*-Hex-CH_2 (**C**)	"	**cC**	85/15	68
1c	*i*-Bu	Bn	"	**cB**	83/17	80
1d	Ph	*i*-Pr (**D**)	"	**dD**	75/25	72
1d	Ph	Bn	"	**dB**	90/10	75
1e	Bn	*i*-Pr	"	**eD**	75/25	75
1e	Bn	*i*-Pr	$Zn(BH_4)_2$	**eD**	65/35	63
1e	Bn	*n*-Bu	$NaBH_4$	**eA**	75/25	75
1f	*n*-Bu-C≡C-CH_2	Bn	"	**fB**	88/12	66

We then turn our attention toward the substituted nitriles **1b–f**. When using Grignard reagents in ether[13] and sodium borohydride as reducing agent, we obtained mainly the all *syn* aminodiols **2** in addition to a small amount of their stereoisomers **3**, as shown by NMR analysis (Table 1). After protection of the amino group, the two diastereomers were easily separated to give the compounds **4** and **5** in good yields.[14] Moreover, this separation was facilitated by the fact that, in all cases, the all *syn* isomer **4** was eluted first.

The best results were obtained using sodium borohydride as a reducing agent in presence of methanol.

However, it was also possible to reduce the magnesium salt directly with zinc borohydride in ether but, in this case, the diastereomeric excess was lowered.

The relative configuration of compounds **4dB**, **4eD** and **4dD** was determined after deprotection of the diol moiety and its oxidative cleavage, followed by esterification of the resulting *N*-Boc amino acids using diazomethane (Scheme 2). The specific rotations of compounds **6** allowed us to determine the absolute configuration of the carbon in position 3, according to the values found in literature for Boc-L-Val-OMe and Boc-L-Phe-OMe.

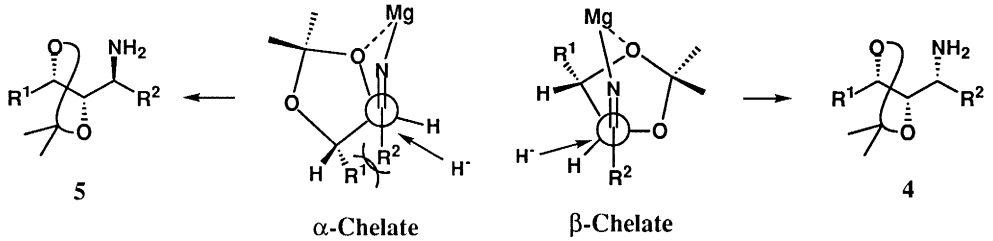


Scheme 2.

This configuration was confirmed using chiral GC by comparison of compounds **6** with authentic samples of L- and racemic Boc-Val-OMe and Boc-Phe-OMe.[15] These amino esters were found to be enantiomerically pure by these methods.

The configuration of the other compounds of structure **4** was determined by ^{1}H and ^{13}C NMR on the basis of the differences observed between **4dB**, **4eD**, **4dD** and their respective diastereomer **5**. In all cases, the proton attached to the nitrogen atom was found in $CDCl_3$ at lower field for the all *syn* diastereomer **4** (δ_{NH}(**4**)–δ_{NH}(**5**)=0.5–0.9 ppm)). Moreover, the coupling constant between H-2 and H-3 was smaller for compounds **4** (0.6–1.0 Hz) than for their diastereomers **5** (7.3–9.3 Hz). In ^{13}C NMR, the carbon C-3 appeared also clearly at higher field for the all *syn* compounds ($\delta_{C\text{-}3}$(**4**)–$\delta_{C\text{-}3}$(**5**)≥ -3 ppm).

The stereoselectivity observed may be explained by a competition between an α- and a β-chelation. Indeed, after addition of the Grignard reagent, the magnesium atom of the magnesioimine may be chelated to the oxygen in position α or β. The formation of the α-chelate is probably disfavoured by the steric hindrance between the R^1 and the R^2 groups when R^1 is not a hydrogen (Scheme 3). Moreover, in the β-chelate, a C–O bond is perpendicular to the C=N plane. In such case, according to the Felkin–Ahn model, the resulting overlap between the π^*_{CN} and the σ^*_{CO} orbitals leads to a more electrophilic imine by lowering the LUMO energy.



Scheme 3.

However, given that methanol was added before sodium borohydride, it must be pointed out that the true nature of the intermediate (i.e. magnesioimine or free imine) is not clearly defined. So, the stereoselectivity may also be explained by α- or β-chelation between the free imine and one of the oxygen atoms through an intramolecular hydrogen bond.

In conclusion, the reductive alkylation of acetonide protected *syn* 2,3-dihydroxynitriles constitutes a new and efficient way to prepare all *syn* 1,3-disubstituted 3-amino-1,2-diols in high enantiomeric purities.

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13. It must be outlined that the Grignard reagents do not react with nitriles **1** in pure THF, a result which is perhaps due to the formation of agregates. The reaction is however possible in a 2:1 mixture of diethyl ether and THF.
14. In a typical experiment, 4.5 mmol of Grignard reagent in ether was added to a solution of 3 mmol of dialkoxynitrile **1** in dry ether at −15°C. The mixture was stirred at rt until completion of the reaction as indicated by TLC (4–6 h). After cooling at −15°C, 3 ml of anhydrous methanol were added followed by 6 mmol of solid $NaBH_4$. The mixture was vigorously stirred overnight at rt, then carefully quenched with H_2O and extracted with ether. The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was dissolved in THF, then aqueous 1N NaOH (3.3 ml) and of Boc_2O (3 mmol) were added. After vigorous stirring for 6 h, the mixture was diluted with ether. The organic phase was washed with 1N HCl and the combined aqueous phases were extracted with ether. The combined organic phases were dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography to give the protected aminodiols **4** and **5**. Selected data for compounds **4** and **5**: $[\alpha]_D^{20}$ **4bB** +15.5 (c 1.88, $CHCl_3$); **5bB** −20.8 (c 0.72, $CHCl_3$); **4cC** +17.9 (3.07, $CHCl_3$); **4cB** +11.7 (c 2.29, $CHCl_3$); **4dD** −6.3 (c 2.29, $CHCl_3$); **5dD** −53.4 (c 1.46, MeOH); **4dB** −7.0 (c 2.58, $CHCl_3$); **5dB** −71.0 (c 1.55, MeOH); **4eD** +2.9 (c 3.36, MeOH); **5eD** −16.8 (c 1.90, MeOH); **4eA** +3.1 (c 2.54, MeOH); **5eA** −37.1 (c 2.93, $CHCl_3$); **4fB** +10.0 (c 1.09, MeOH). ^{1}H NMR (400 MHz) δ ppm ($CDCl_3$) **4dD** 0.86 (d, 3H, *J*=6.7 Hz), 0.91 (d, 3H, *J*=6.8 Hz), 1.51 (s, 9H), 1.54 (s, 3H), 1.57 (s, 3H), 1.73 (m, 1H), 3.50 (ddd, 1H, *J*=0.6, 7.4, 10.5 Hz), 3.84 (dd, 1H, *J*=0.6, 8.6 Hz), 4.66 (d, 1H, *J*=8.7 Hz), 4.96 (d, 1H, *J*=10.4 Hz, NH), 7.4 (m, 5H). **5dD** 0.80 (d, 3H, *J*=6.9 Hz), 0.91 (d, 3H, *J*=6.9 Hz), 1.44 (s, 9H), 1.51 (s, 3H), 1.57 (s, 3H), 2.17 (septd, 1H, *J*=6.9, 3.2 Hz), 3.77 (dd, 1H, *J*=7.6, 9.3 Hz), 3.87 (td, 1H, *J*=3.2, 9.5 Hz), 4.01 (d, 1H, *J*=10.4 Hz, NH), 4.93 (d, 1H, *J*=7.6 Hz), 7.2–7.4 (m, 5H). ^{13}C NMR (50 MHz) δ ppm ($CDCl_3$) **4dD** 19.09 (CH_3), 19.73 (CH_3), 27.09 (CH_3), 27.26 (CH_3), 28.53 (3×CH_3), 32.21 (CH), 52.96 (CH–N), 79.33 (C), 80.02 (CH), 83.45 (CH), 109.08 (C), 126.62 (2×CH), 128.17 (CH), 128.65 (2×CH), 137.69 (C), 156.33 (C); **5dD** 15.56 (CH_3), 19.74 (CH_3), 27.13 (CH_3), 27.38 (CH_3), 28.48 (3×CH_3), 28.99 (CH), 57.71 (CH–N), 79.28 (C), 83.04 (2×CH), 109.40 (C), 127.58 (2×CH), 128.28 (CH), 128.53 (2×CH), 139.18 (C), 155.73 (C).
15. The *N*-Boc amino esters were analyzed on a 25 m Chirasil-D-Val column (Chrompack) on which such compounds with L configuration are eluted in first.