Usage of α-picoline borane for the reductive amination of carbohydrates

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This article is dedicated to Profs. Rita H. Rossi, Julio C. Podestá, Manuel González Sierra and Oscar S. Giordano, to recognize their achievements in organic chemistry and their contributions in the development of the field in Argentina

DOI: http://dx.doi.org/10.3998/ark.5550190.0012.716

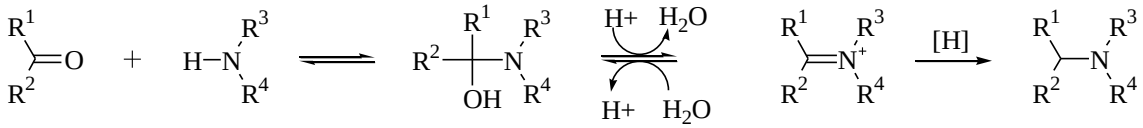
Abstract

The reaction of reductive amination, widely used for carbohydrates, was reviewed in our lab, especially in the context of the analytical determination of carbohydrate enantiomers. The best conditions for the technique have been evaluated, showing that under optimal working conditions it is possible to use α-picoline borane as a reducing agent instead of sodium cyanoborohydride without affecting the selectivity or the yield. The main reason for the variation of the technique was that, in the presence of acetic acid, secondary epimeric products were produced with α-picoline borane due to an Amadori rearrangement. This new modification assures lower toxicity, and thus a more environmental-friendly reaction system. Preparative scale synthesis can also be efficiently made with this reducing reagent.

Keywords: Carbohydrates – Reductive Amination – Picoline borane – Amadori rearrangement

Introduction

The reaction of reductive amination, widely used for organic synthesis, allows for the conversion of the carbonyl group into amines. The reaction begins with the coupling of an aldehyde or ketone and a primary or secondary amine to give an imine, which is then reduced to give a secondary or tertiary amine[1,2] (Scheme 1).



Scheme 1. Reductive amination reaction.

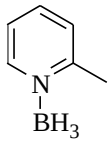
The reaction can be carried out either in a "one-pot" system, where the formation of the imine and its reduction product occur in only one operational stage, or stepwise, where the intermediate imine is isolated, and reduced in a second stage.

The selection of reducing agents in this type of reactions is critical, since they must reduce selectively the imine without affecting significantly the original carbonyl compound or other reducible groups present. A large number of reducing agents have been developed, though many of them present unwanted properties in terms of selectivity, secondary reactions, reaction conditions, safety hazards, and toxicity.

The catalytic hydrogenation is the most employed reductant for imines in large scale syntheses,[3] although it is limited to molecules which do not carry double bonds or other reducible groups under hydrogenation conditions. For laboratory scale, sodium cyanoborohydride ($NaBH_3CN$), among other hydrides, is the reagent most employed for reductive amination:[4] it is highly selective, soluble in many solvents, and stable in acid medium (up to pH 2).[1] Cases *et al.*[5] found that the optimum pH for the reductive aminations of galactose and 1-amino-2-propanol was 4. Nevertheless, $NaBH_3CN$ generates highly toxic products such as HCN or NaCN during the reaction or work-up, and thus should not be recommended for medium or large scale reactions, and even less in the actual context of "green chemistry". Sodium triacetoxyborohydride ($NaBH_3(OAc)$)[6] has also been employed, but mostly in non-protic solvents, since in methanol or water it reduces the carbonyl groups, decomposes, and gives flammable subproducts.[7] Pyridine borane (Pyr-BH_3)[8-10] was the most representative aminoborane employed, but it is unstable, and decomposes causing fire; even explosions were reported.[11]

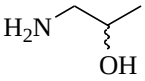
Following an initial finding of Oshima and coworkers,[12] we have developed in our lab a technique for the chromatographic resolution of enantiomeric sugars by reductive amination with chiral amines (*i.e.* by generation of diastereomers), using $NaBH_3CN$ as the reducing agent.[5,13] However, we decided now to try another less toxic reductant: the substitute chosen was the α-picoline borane (**Pic-BH_3**, Scheme 2). This reagent appeared on the market in 2004.[11] Sato *et al.* showed its smooth working conditions in different solvents (including water), no generation of toxic wastes, stability up to 150ºC, high selectivity and low cost.[11] The use of water in the reaction medium would be a remarkable advantage, especially at an industrial level.

Herein, we introduce the use of α-picoline borane as a replacement of sodium cyanoborohydride in the reductive amination employed for the determination of the absolute configuration of the monosaccharides present in polysaccharides or glycosides, and its extension to the synthesis of aminodeoxyalditols in larger amounts.



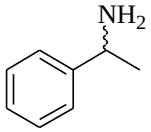
a-Picoline borane

Pic-BH_3



(±)-1-Amino-2-propanol

AP



(±)-*a*-Methylbenzylamine

MBA

Scheme 2. Main reagents used in this work and their acronyms.

Results and Discussion

In order to evaluate the viability of the usage of α-picoline borane (**Pic-BH_3**) instead of sodium cyanoborohydride for the reductive amination used in the determination of the absolute configuration of monosaccharides,[5] it was first decided to try the reaction of D-galactose and a) (±)-1-amino-2 propanol (**AP**), and b) (±)-α-methylbenzylamine (**MBA**, Scheme 2), using the reaction conditions described by Sato *et al*.,[11] *i.e.* 1:1:1.2 ratio of sugar, amine and reducing agent, both in water and methanol (containing 10% of AcOH). In order to follow the reaction by gas chromatography (GC), the reaction mixture was treated with acetic anhydride/ pyridine. In this way, a mixture of peracetylated aminodeoxyalditols, peracetylated galactitol and cyclic forms of penta-*O*-acetyl-D-galactose was obtained. In water, after 2 h only 10% of the reaction product (aminodeoxyalditol) was obtained with **AP**, and 1% with **MBA**. The remainder was mostly galactose, with small amounts of galactitol. The methanolic reagent showed no improvement in the reaction with **MBA** but with **AP** a 74% of diastereomeric aminodeoxyalditols were obtained, together with 20% of galactose and 5% of galactitol. These results suggested that changing the reaction conditions, the yields of aminodeoxyalditols can be improved. They also show that the reductant hardly reacted with the aldehyde group of the monosaccharide to give the corresponding alditol.

Subsequently we decided to modify the reaction with **Pic-BH_3** to the conditions used when reducing with $NaCNBH_3$.[5,13] The reaction occurs efficiently (Table 1) with **AP** and either reducing agent (yields > 90%). The reaction of **MBA** and **Pic-BH_3** showed the appearance of a small but significant amount of unreacted galactose. The galactose/**AP** diastereomers appeared in an equimolar ratio, whereas those with **MBA** presented stereoselectivity, as already reported.[5,13] The most interesting fact was, however, the appearance of a minor peak with **MBA** (a resolved pair with **AP**) after the reaction with **Pic-BH_3** which was absent when working with $NaCNBH_3$. The analysis of those peaks by GC/MS revealed that they were also peracetylated 1-amino-1-deoxyalditols, but (as they had different retention time) becoming from a different hexose. After discarding the presence of impurities in the Gal standard, we thought that a transposition of the double bond of the imine towards the C1-C2 hexose bond might occur, thus originating a loss of the C2 chirality. When this chirality is regenerated, it occurs with partial epimerization.

On the first step of the reaction, the carbonyl and the amino group build reversibly an imine which can, after enolization towards C1-C2 of the sugar, generate a 1-amino-1-deoxyketose.[14-17] This reaction is known as Amadori rearrangement (Scheme 3). In the current reductive amination reaction, if a fraction of the imine transposes the double bond by the Amadori rearrangement (Scheme 3), this alkylaminodeoxyketose can (in the presence of more reductant) generate the epimeric 1-alkylamino-1-deoxyalditols by two different pathways (Scheme 4): a) direct reduction of the ketose, generating a C2 stereocenter with two possible configurations, and b) tautomerization of the double bond back to C1 to generate two epimeric imines, which are reduced to two different 1-alkylamino-1-deoxyalditols.

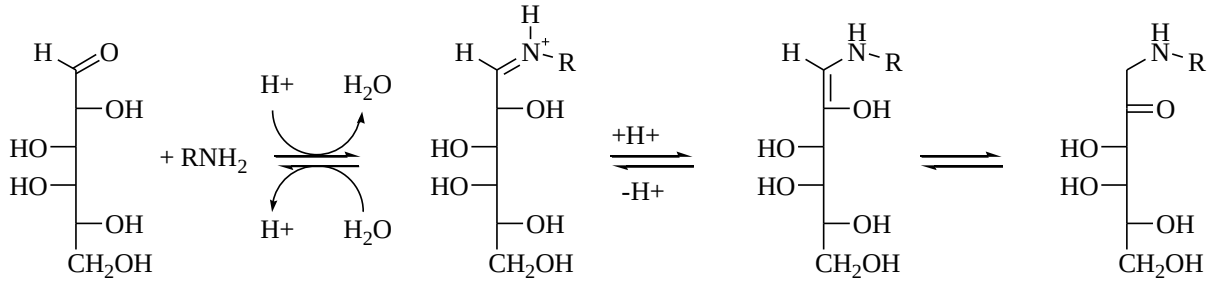
Table 1. Product ratio[a] after reductive amination between D-Gal and racemic **AP** or **MBA** using two different reducing agents

Conditions/ Reagents[b]	**Molar ratio (%)**				
	D-Gal	Galactitol	"Unknown"	Aminogalactitol	
				D/(*S*)	D/(*R*)=L/(*S*)[b]
Pic-BH_3					
MeOH:AcOH (10:1)-1 h-65 ºC					
D-Gal + **AP** 1:5	-	2.3	4.9[c]	46.6	46.2
D-Gal + **MBA** 1:5	8.3	3.3	2.3[d]	51.6	34.4
$NaCNBH_3$					
MeOH:AcOH (13:1)-1 h-65 ºC					
D-Gal + **AP** 1:5	1.3	2.9	–	48.8	47.0
D-Gal + **MBA** 1:5	2.0	6.0	–	58.0	34.0

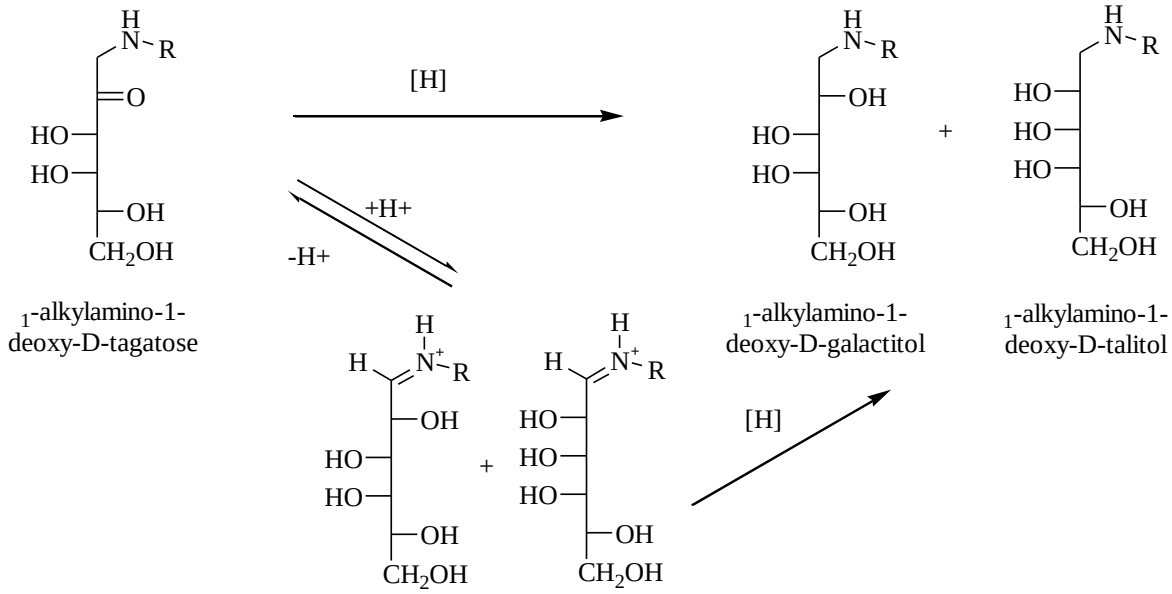
[a] Determined by GC after acetylation. The reaction was carried out with a molar ratio **Pic-BH_3**/Gal of 1.2. [b] D/(*R*) =L/(*S*) are enantiomers chromatographically equivalent. [c] Two equimolar peaks with relative retention times of 0.992. [d] Only one peak.

Thus, if this explanation holds, partial or total epimerization of C2 can occur. In this case, D-galactose would originate galactose and talose aminodeoxyalditol derivatives by a combination of reactions summarized in Scheme 5. Even though the Amadori product is built from successive reversible steps (K_1+K_3), previous studies showed that the regeneration of the imine is very slow (K_5), especially if those products are stabilized by formation of the corresponding cyclic ketal.[17] Therefore, it is most likely to obtain the epimers in C2 by direct reduction of the 1-amino-1-deoxy-2-ketoses (Scheme 5, K_4). However, this can only happen if **Pic-BH_3** has reducing power over ketones. This activity was reported for other aminoboranes,[7] but not for **Pic-BH_3**. Therefore, we have carried out an experiment to determine whether the **Pic-BH_3** could reduce D-

fructose. Using reaction conditions similar to those used for reductive amination, it was observed, by gas chromatography, that nearly half the fructose was reduce to mannitol and galactitol, suggesting that the K_4 step (Scheme 5) is possible with this reductant.



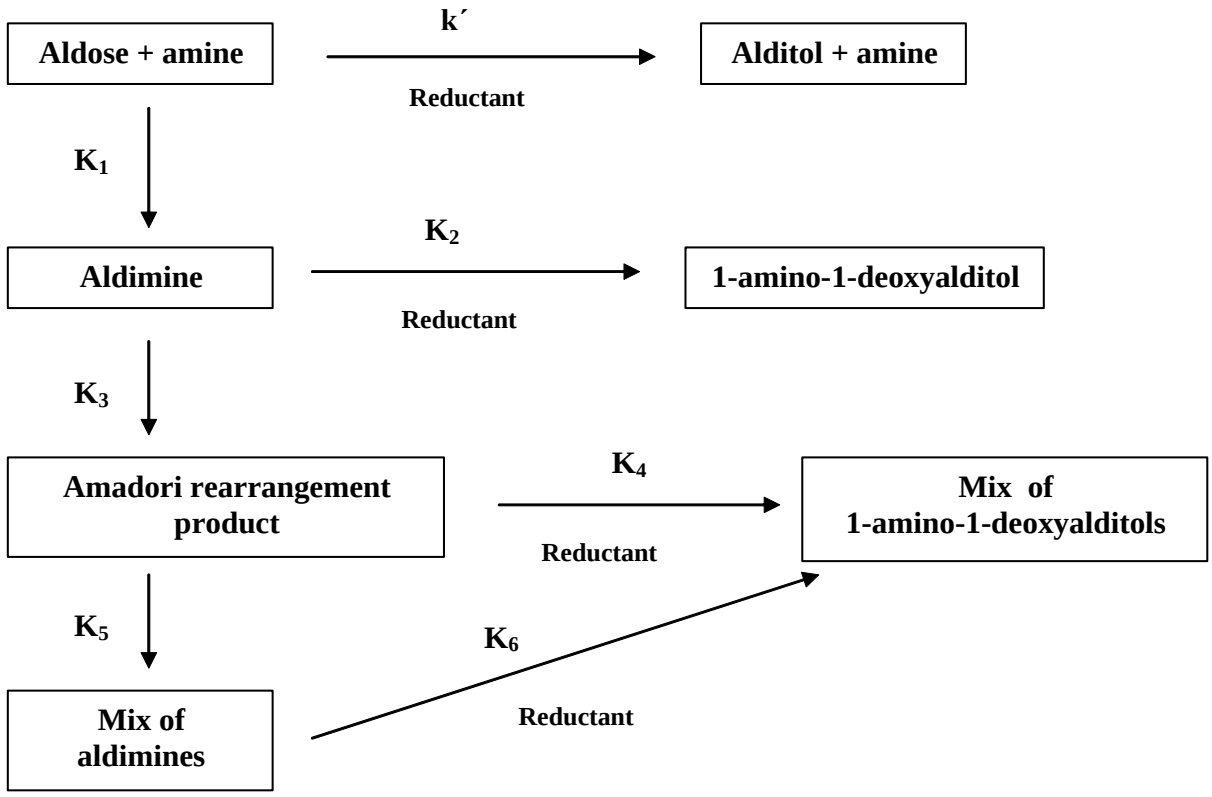
Scheme 3. Amadori rearrangement (exemplified for D-Gal and a generic amine).



Scheme 4. Possible reduction pathways of a 1-alkylamino-1-deoxyketose.

In order to confirm the hypothesis that the unknown peaks became from epimerization of the galactose, we decided to carry out the reductive amination reaction using commercial D-talose (*i.e.* the C2 epimer of D-galactose) and **Pic-BH3** as reductant. By GC of the peracetylated derivatives made with racemic **AP**, we were able to observe the separation of the two diastereomers, whose retention times agree with those determined for the unknown 1-amino-1-deoxyhexoses peaks found in the original reaction with galactose (Table 1). With chiral **AP**, we have determined that the talose isomer that eluted with a lower retention time corresponded to the D-Tal/(*S*)-amine adduct. Minor peaks corresponding to the galactose derivative appeared, proving that the partial epimerization of the talose into the galactose was also occurring.

The diastereomers made from racemic α-methylbenzylamine (**MBA**) and D-talose could not be separated by gas chromatography under the conditions used for these derivatives (Table 1). Only one peak appears with a retention time matching (as expected) the minor peak found when analyzing the 1-deoxy-1-(1´-phenylethylamino)-galactitol.



Scheme 5. Possible reaction pathways between an aldose and an amine in presence of a reductant.

These facts showed that our hypothesis was correct: there was a generation of talose derivatives as secondary products in the reactions with galactose, coming from the epimerization of C2 mediated by Amadori rearrangement.

The **Pic-BH$_3$** reductive amination was attempted with rhamnose and quinovose, other two C2 epimers which are commercially available. Once again, we were able to observe, when derivatizing each one separately with chiral **AP**, the corresponding interconversion. In the case of the reaction with quinovose, the epimerization was especially important, since *ca.* 21% of the original monosaccharide was transformed into the rhamnose derivative (as determined by GC). Assuming that the reduction is not diastereoselective, this implies that *ca.* 40% of the imine of quinovose rearranged to the Amadori product. This result shows that it is not possible to predict the proportion of epimerization in the reduction reaction.

From these results, we can conclude that $NaCNBH_3$ probably reduces the imine groups at a higher rate than **Pic-BH$_3$** (K_2), since the Amadori rearrangement products are absent with the former reductant (Table 1).

Optimization of the reaction conditions

The epimerization reaction is undesirable for a quantitative assessment of the monosaccharides present in a mixture.[5,13] Thus, in order to be able to use **Pic-BH$_3$** as a safe replacement for $NaCNBH_3$, this epimerization has to be avoided.

Using D-galactose and **AP** as the reagents, we have carried out a systematic study of the influence of several factors on the outcome of the reaction (Table 2). In the presence of AcOH, no major influence of time and temperature were found, although a small rise of the epimerization product was found as time and temperature increased (Table 2). The best results were obtained at 40ºC and 1 h of reaction, though a small proportion of epimerized products still appeared. Considering that the other sugars like quinovose yield even more epimerization, the search for new reaction conditions was continued. The reductant amounts were also varied, both at 40 ºC and at 65 ºC (Table 2). The results showed that at either temperature, the amount of reductant did not have any influence on the proportion of 1-amino-1-deoxytalitol. However, at 40ºC, in presence of a great excess of **Pic-BH$_3$**, the amount of galactitol increased, confirming the capacity of the reagent to reduce the carbonyl group, although at a slower rate (k') than those of the formation and reduction of the imine (K_1 and K_2, Scheme 5). Thus the reductant has an appreciable selectivity.

The key factor was acetic acid: its absence yields no epimerization at all (Table 2). These results agree with older studies of Amadori rearrangement.[14] The reaction was repeated with others sugars in absence of acid catalysis, showing that no epimerization occurred in any case. These results show that **Pic-BH$_3$** can be used as a reductant in the technique of enantiomeric determination of monosaccharides,[5] provided that it is carried out in absence of acid to avoid isomerizations. This differs from the reductive amination with $NaCNBH_3$, which requires acid.[5]
Table 3 shows the yields of the reaction (by GC, as compared with an internal standard of peracetylated inositol) using $NaCNBH_3$ or **Pic-BH$_3$**, as well as modifying other reaction factors, now without acid addition.

Table 2. Product ratios[a] obtained after reductive amination between D-Gal and racemic **AP** with **Pic-BH$_3$** using different reaction conditions

Conditions/ Reagents	Molar ratio (%)			
	Galactose	Galactitol	Aminoalditol	
			Tal[b]	Gal[b]
Effect of time of reaction[c]				
0.5 h	1.4	3.2	3.4	92.0
1 h	–	2.3	4.9	92.8
2 h	–	tr.[d]	7.0	93.0
3 h	–	tr.	6.8	93.2
Effect of temp. of reaction[e]				
40 ºC	tr.	2.9	1.0	96.1
50 ºC	1.5	2.5	2.5	93.4
65 ºC	-	2.3	4.9	92.8
Effect of Pic-BH$_3$/Gal ratio				
0.5:1[f]	2.5	2.7	5.2	89.6
1.2:1[f]	-	2.3	4.9	92.8
2.0:1[f]	2.2	2.3	5.9	89.5
1.2:1[g]	tr.	2.9	1.0	96.1
10:1[g]	tr.	8.4	1.1	90.0
Effect of the solvent[h]				
MeOH	2.0	2.0	–	96.0
MeOH:AcOH (13:1)	–	2.3	4.9	92.8
MeOH:AcOH (4:1)	1.6	4.4	3.2	90.6

[a] Determined by gas chromatography after acetylation. [b] Diastereomers D/(*S*) + (D/(*R*) =L/(*S*)). [c] MeOH:AcOH 13:1, 65 ºC, 1.2 mols of **Pic-BH$_3$** and 5 mols of **AP** per mol of D-Gal. [d] Traces, percentage less than 1%. [e] MeOH:AcOH 13:1, 1 h, 1.2 mols of **Pic-BH$_3$** and 5 mols of **AP** per mol of D-Gal. [f] MeOH:AcOH 13:1, 1 h, 65 ºC, 5 mols of **AP** per mol of D-Gal. [g] MeOH:AcOH 13:1, 1 h, 40 ºC, 5 mols of **AP** per mol of D-Gal. [h] Reaction for 1 h at 65 ºC, 1.2 mols of **Pic-BH$_3$** and 5 mols of **AP** per mol of D-Gal

Table 3. Product ratios[a] and yields obtained after reductive amination[b] between D-Gal and racemic **AP** using different reaction conditions

Conditions/ Reagents	Molar ratio (%)				Yield (%)[b]
	Galactose	Galactitol	Aminogalactitol		
			D/(*S*)	D/(*R*)=L/(*S*)[c]	
NaCNBH$_3$[d]					
D-Gal / **AP** 1:5	1.3	2.9	48.8	47.0	98
Pic-BH$_3$[d]					
D-Gal / **AP** 1:5	1.8	2.0	50.0	46.2	97
Effect of D-Gal/AP ratio[e]					
1:1.2	5.5	3.8	90.7[f]		93
1:3.0	4.8	3.2	92.0[f]		94
1:5.0	3.0	-	97.0[f]		97
Effect of temperature[e]					
40 ºC	27.7	1.2	71.1[f]		77
50 ºC	10.7	1.2	88.2[f]		83
65 ºC	3.0	-	97.0[f]		97

[a] Determined by gas chromatography after acetylation. [b] Molar yield taking peracetylated inositol as 100. [c] D/(*R*) =L/(*S*) are enantiomers chromatographically equivalent. [d] In the reaction conditions previously determined as optimal. [e] With the remaining reaction conditions previously determined as optimal with **Pic-BH$_3$**. [f] Diastereomers D/(*S*) + (D/(*R*) =L/(*S*)).

The reaction yields are almost identical for both reducing agents (Table 3). The small proportions of unreacted galactose and galactitol were also very similar for both reductants, and no epimerization was observed. The optimal amine/sugar ratio was investigated, as the earlier **Pic-BH$_3$** reductions[11] were carried out with equimolar amounts of carbonyl compound and amine. Table 3 shows that the best yields, and the lower amounts of side-products are obtained using a five-fold excess of amine over the carbonyl compound, as expected[1,5] considering that equimolar amounts might lead to reaction of the product (a secondary amine) with another carbonyl group to generate a tertiary amine. Besides, it has been shown (Table 3) that a higher temperature is needed to provide a complete reaction, as lower ones give rise to large amounts of unreacted monosaccharides. These results show that in optimal working conditions it is possible to use α-picoline borane as a reducing agent instead of sodium cyanoborohydride without affecting the selectivity or the yield.

Other applications

In order to test this modification of the technique, the configuration of the monosaccharides of the raw corallinan extracted from the red seaweed *Corallina officinalis* was assessed. This polysaccharides was chosen since it contains a great variety of monomethylated galactoses.[18] The sugars obtained after hydrolysis and **Pic-BH$_3$**/**AP** reductive amination were D-Xyl (22%), 2-*O*-Me-Gal (5%), 4-*O*-Me-D-Gal (2 %), 4-*O*-Me-L-Gal (2 %), D-Glc (9%), D-Gal (35%) and L-Gal (25%). These figures agree with the xylose-substituted agaran structure of this polymer,[19] with previous reports,[18] and with the results of the same sample derivatized using $NaCNBH_3$. The configuration of the 2-*O*-Me-Gal cannot be determined using **AP**.[5]

The reductive amination with **Pic-BH$_3$** was also tested with other amines, like α-methylbenzylamine, propylamine, butylamine and octylamine, in methanol without AcOH. No epimerization was found to occur in either case. The synthesis was also carried out in preparative scale using D-galactose and (*S*)-**MBA**. The isolated yield was 73% and the product was characterized by the usual spectroscopical techniques (see Experimental Section).

The reductant was also used in the determination of the configuration of 3,6-anhidrogalactose,[13] which requires more subtle conditions, on a commercial κ-carrageenan (which ideally contains similar amounts of D-Gal and 3,6-An-D-Gal). **MBA** was used as the chiral amine. Both the reactions with $NaCNBH_3$ and **Pic-BH$_3$** (each in its optimal conditions) show negligible amounts of alditols or unreacted galactose. The yields relative to inositol were 84 and 80%, respectively. The difference is quite small, although observable in other experiences with **MBA**. Both reductants showed a slight excess of 3,6-AnGal over Gal.

Conclusions

The current results show that α-picoline borane can be used for the technique of configurational determination of sugars as a safe replacement of $NaCNBH_3$, without affecting the results. This new modification assures lower toxicity, and thus a more environmental-friendly reaction practice in the context of green chemistry.

The reactions conditions use for α-picoline borane in the reductive amination reaction of monosaccharides were modified in comparison to those employed for $NaCNBH_3$. The main reason for the modification was that, in the presence of acetic acid, secondary epimeric products were produced due to an Amadori rearrangement.

The yields of the reductive amination reactions with α-picoline borane in methanol without acid are comparable to those obtained with $NaCNBH_3$, either in a monosaccharide standard system, or for the analysis of polysaccharides. Preparative synthesis is also possible with good yields of isolated product.

Experimental Section

Reagents and solvents. The α-picoline borane (**Pic-BH$_3$**) was purchased from Junsei Chemical Co., Japan and from Sigma-Aldrich. All the remaining reagents, standards and solvents were of analytical grade, and were purchased in Sigma-Aldrich, Fluka, or Merck. The sample of commercial κ-carrageenan was purchased from Sigma.

Reductive amination of galactose

The preliminary experiments were carried out using either the procedure of Sato *et al*.[11] (Method A) or Cases *et al*.[5] (Method B). The amines tested were (±) 1-amino-2-propanol (**AP**) and (±)-α-methylbenzylamine (**MBA**). The products were always analyzed by gas chromatography as peracetylated aminoalditols, using the chromatographic conditions shown later.[5]

Method A. 0.027 mmol (5 mg) of D-Gal and 0.027 mmol (5 mg) of inositol (internal standard) were added into 150 μl of a mixture of H_2O-AcOH 10:1. Then, 0.027 mmol of amine and 0.027 mmol (2.89 mg) of **Pic-BH$_3$** were added. The mixture was stirred for 2 h at room temperature and then it was acidified with TFA 3M. The solution was evaporated off, washed with water (3 x 0.5 ml) and the residue left on a vacuum desiccator overnight. Then, the residue was acetylated by adding 1 ml of a mixture of Ac_2O-Pyr (1:1) for 45min at 100ºC. Once the solution cooled down, it was extracted with $CHCl_3/H_2O$. The aqueous phase was reextracted with $CHCl_3$. The organic extracts were joined and washed with 1 ml of satd $NaHCO_3$ sn (x 3) and with 1 ml of water (x 2). Finally, the organic phase was dried with Na_2SO_4 (anh.) and evaporated off. The residue was redissolved in $CHCl_3$ to inject into the gas chromatograph apparatus. The same procedure was carried out using a MeOH/AcOH 10:1 mixture as solvent.

Method B. The reductive amination was carried out with 0.006 mmol (1 mg) of D-Gal as described by Cases *et al*.[5], but using **Pic-BH$_3$** as reductant and adding 0.006 mmol (1 mg) of inositol as an internal standard. We added to the vial consecutively: 20 or 32 μl of a solution 1:8 (v/v) of **AP** or **MBA**, respectively, in MeOH (5 mols amine/mol Gal), 17 μl of a AcOH/MeOH solution 1:4 (v/v) and 13 μl of **Pic-BH$_3$** 5% (w/v) in MeOH (1.2 mols reductant/mol Gal). The reaction was heated at 65ºC for 1 h, allowed to cool down, and acidified with TFA 3M up to pH 1-2. The remaining work up was carried out as depicted for the method A.

Study of the reactions conditions using α-picoline borane. This set of reactions was carried out with D-Gal and **AP**, using the method B modified in order to test for different temperatures (40-65 ºC), reaction times (0.5-3 h), reducing agent proportions (0.5-2 equivalents), proportion of AcOH and amine, etc.

Optimized conditions for the reductive amination with α-picoline borane. To 0.027 mmol (5 mg) of reducing sugar it was consecutively added: 50 μl of MeOH, 0.135 mmols of amine and 0.03 mmol (3.21 mg) of **Pic-BH$_3$**, and the mixture was heated at 65 ºC in a closed vial for 1 h. After cooling down, drops of TFA 3M were added up to pH 1-2. The solutions were dried, washed with water (3 x 0.5ml) and with MeOH (5 x 0.5 ml). The residue was left on a vacuum desiccator with overnight, and then the products were acetylated and worked up as described in Method A.

Reduction of fructose. Fructose was submitted to the conditions described in Method B, but without adding the amine.

Analysis of polysaccharides. The polysaccharide from *Corallina officinalis*[18] was hydrolyzed with 2 M TFA (90 min, 120 ºC) before analysis of the corresponding monosaccharides, whereas the κ-carrageenan was submitted to a reductive hydrolysis as described by Navarro and Stortz,[13] but using **Pic-BH3** instead of $NaCNBH_3$.

Gas-liquid chromatography. It was carried out in a Hewlett Packard 5890A Apparatus equipped with a flame ionization detector (FID) and a HP 3395 integrator. The carrier gas was N_2 (0.8 ml/min) and the split relation was close to 80:1. The injector and detector temperature were set to 270 ºC. The products from the reductive amination were analyzed with an Ultra 2 column (Hewlett-Packard, 50 m, 0.36 mm i.d., 0.17μm film width). For peracetylated 1-deoxy-1-(2'-hydroxypropylamino)alditols the program ramp was programmed from 180 to 220 ºC at 4 ºC/min, hold at 220 ºC for 2 min, from 220 to 250 ºC at 1 ºC/min, then hold at 250 ºC for 20 min. For peracetylated 1-deoxy-1-(2'phenylethylamino)alditols the program started from 180 to 220 ºC at 4 ºC/min, hold at 220 ºC for 2 min, from 220 to 270ºC at 1 ºC/min, and hold at 270 ºC for 20 min.

Synthesis of (*S*)-1-deoxy-1-(1'-phenylethylamino)-D-galactitol. To a solution of 0.33 mmol (60 mg) of D-Gal in 4 ml of MeOH, 214 μl of (*S*)-α-methylbenzylamine (5 mols amine/mol Gal) and 39 mg of **Pic-BH3** (1.25 mols reductant/mol Gal) were added. The reaction mixture was heated at 65 ºC for 3 h. The solvent was removed under reduced pressure. The product was purified using an Amberlite IR-120 (H^+) column: after washing with 75 ml water, the product was eluted with 75 ml of 1M NH_3. After exhaustive perevaporation at reduced pressure, the sample was obtained as a white solid by freeze-drying. Yield 73% (69.3 mg), decomposes at 209-211ºC. ^{1}H NMR (500.1 MHz, D_2O + 1 drop HCl): δ_H 1.29 (3H, d, $J_{1',2'}$ = 6.6 Hz, CH_3), 2.49 (1H, dd, $J_{1a,2}$ = 4.1 Hz, $J_{1a,1b}$ = 12.6 Hz, H1a), 2.53 (1H, dd, $J_{1b,2}$ = 8.3 Hz, $J_{1a,1b}$ = 12.6, H1b), 3.39 (1H, dd, $J_{2,3}$ = ca. 1 Hz, $J_{3,4}$ = 9.3 Hz, H3), 3.50 (1H, dd, $J_{3,4}$ = 9.3 Hz, $J_{4,5}$ = ca. 1 Hz, H4), 3.55 (2H, d, $J_{5,6}$ = 6.4 Hz, H6a & H6b), 3.78 (1H, q, $J_{1',2'}$ = 6.6 Hz, HCPh), 3.81 (1H, dt, $J_{4,5}$ = ca. 1 Hz, $J_{5,6}$ = 6.4 Hz, H5), 3.90 (1H, ddd, $J_{1a,2}$ = 4.2 Hz, $J_{1b,2}$ = 8.3 Hz, $J_{2,3}$ = ca. 1 Hz, H2), 7.22-7.36 (5H, m, Aromatic H). ^{13}C NMR (125.8 MHz, D_2O + 1 drop HCl, from HSQC spectrum): δ_C 22.0 (CH_3), 49.4 (C1), 57.0 (CHPh), 63.1 (C6), 68.2 (C2), 69.4 (C4), 70.1 (C5), 71.0 (C3), 126.8, 127.5 and 128.8 (Aromatic C). HRMS (ESI): Calcd. for $C_{14}H_{24}NO_5$: *m/z* 286.16490 ; found : *m/z* 286.16585.

Acknowledgements

The authors are indebted to Dr. R. Erra Balsells for setting up the first purchase of α-picoline borane in Japan, and to Dr. E. A. Rúveda (IQUIOS-UNR) for helpful discussions. V.A.C. has a fellowship from the University of Buenos Aires, whereas D.A.N. and C.A.S. are Research

Members of the National Research Council of Argentina (CONICET). This work was supported by grants from UBA (X-214) and CONICET (PIP 5699 and 0559/10).

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