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One-pot synthesis of vicinal aminoalkanols from sugar aldehydes

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ABSTRACT

A novel synthetic method of carbohydrate derived vicinal aminoalcohols, from sugar aldehydes and bromonitroalkanes, has been developed. It involves an indium-catalyzed one-pot Henry reaction and nitro group reduction, and proceeds with a remarkably high anti-selectivity. The reaction of the intermediate aminoalcohols with alkylating agents furnished the corresponding carbohydrate-based tertiary aminoalcohols with excellent stereoselectivity. This very simple methodology allows easy access to families of *N*,*N*-dialkylated vicinal aminoalkanols, useful intermediates in the synthesis of derivatives of biological interest and sugar-based stereodifferentiating agents for asymmetric catalysis.

1. Introduction

In the past several years there has been increased pressure on the synthetic community to use environmentally benign or 'green' methods in synthesis. In this regard, the interest in the development of one-pot reactions for the sustainable synthesis of organic compounds has grown exponentially.[1] The use of one-pot conversions, reactions taking place without intermediate recovery steps, drastically reduces operating time and costs as well as consumption of solvents and energy.[2] In this context, reductive one-pot reactions involving carbonyl compounds and nitronates as carbon nucleophiles would be particularly attractive in assembling carbon–carbon bonds around the carbonyl group and directly generating a 1,2-aminoalkanol function.

The 1,2-aminoalkanol moiety is a structural component, which can be found in many naturally occurring molecules. For example, the vicinal aminoalkanol functionality is found in polyoxamic acid, a structural constituent of the nucleoside antibiotic polyoxin,[3] in indolizine alkaloids, such as 1,2-dihydroxyindolizine,[4] and in the potent antifungal sphingosine.[5] On other hand, chiral 1,2-aminoalkanols serve as useful intermediates in the synthesis of several natural products, as well as chiral auxiliaries and ligands for asymmetric synthesis.[6]

Sugar-derived 1,2-aminoalkanols are a particularly relevant family of compounds, not only for their usefulness as intermediates in the preparation of carbohydrate derivatives of biological interest, but also for their potential as stereodifferentiating agents in asymmetric catalysis.[7] Taking into account their importance in synthesis and biology, a short and reliable procedure for the multigram preparation of carbohydrate-based vicinal aminoalkanols would be of great interest. Although sugar-derived 1,2-aminoalcohol building blocks are present in the literature,[8] more efficient and practical routes that allow large-scale preparations reducing the environmental impact are still needed.[9]

In connection with our interest in the application of Barbier-type reactions to carbohydrate chemistry,[10] we have recently described[11] the efficient preparation of nitrosugars by means of the indium promoted addition of bromonitroalkanes to sugar aldehydes.[12] We have also described an indium-catalyzed version of the reaction, in which an excess of zinc was used as secondary reducing agent.[13] It is known that, in the presence of a proton source, zinc alone or in the presence of a catalytic amount of indium can reduce the nitro group to an amino group.[14] Then, we reasoned that adding a proton source to the reaction mixture, we could complete the one-pot Henry reaction-nitro reduction and obtain homologated aminosugars from sugar aldehydes. Herein we report the one-pot synthesis of several aminosugars, potentially useful as synthetic intermediates and ligands for metal catalysis.

2. Results and discussion

In order to set up the optimal conditions to carry out the synthesis of aminosugars, we started our study with the reaction of sugar aldehyde **1a** and bromonitromethane **2a** (Scheme 1). A

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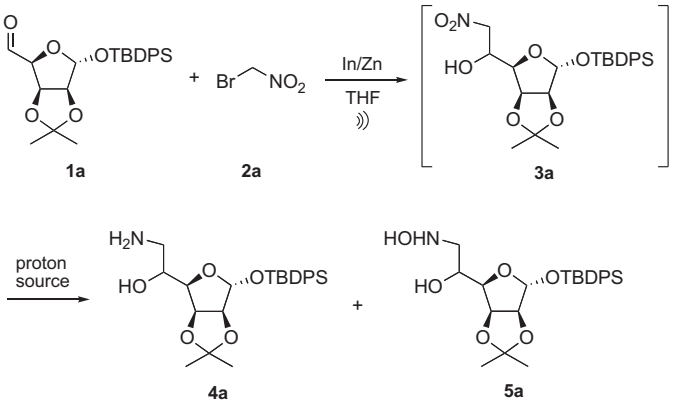


Scheme 1. One-pot synthesis of vicinal aminoalkanol **4a** from aldehyde **1a**.

mixture of aldehyde **1a** (1 equiv), bromonitromethane **2a** (1.2 equiv), indium (0.13 equiv), and zinc (10 equiv) was sonicated for 4 h. Then, after the formation of the corresponding nitrosugar, different conditions for the in situ nitro group reduction were investigated (Table 1).

Table 1
Conditions for the in situ reduction of the nitro group

Entry	Proton source	Conditions	**4a**:**5a**[a]	Yield[b] (**4a**)
1	NH_4Cl satd	rt/3 h	0:1	—
2	NH_4Cl satd	Reflux/3 h	1:1	n.d.
3	HCl 1 M/IPA	Reflux/3 h	1:0	31%
4	HCl 1 M/IPA	rt/3 h	2:1	n.d.
5	HCl 1 M/IPA	rt/12 h	1:0	52%
6	HCl 1 M/IPA	rt/12 h[c]	1:0	64%

IPA=isopropyl alcohol.
[a] Determined by ^1H NMR.
[b] After filtration over silica gel.
[c] Zinc (5 equiv) were added along with the proton source.

Addition of saturated aqueous ammonium chloride as proton source and reaction at room temperature afforded hydroxylamine **5a** as the only product, which is the intermediate product in the reduction of a nitro group to an amino group (entry 1). Rising the temperature to reflux, some of the desired nitroalkanol **4a** was obtained along with hydroxylamine **5a**. The use of 1 M aqueous hydrochloric acid as proton source has proven to be more convenient (entries 3–6). The best procedure in terms of conversion and cleanliness of the crude reaction consider the addition of isopropyl alcohol and diluted hydrochloric acid and the reaction at room temperature for 12 h (entries 5 and 6). Shorter reaction times yielded significant amounts of hydroxylamine **5a** (entry 4). On other hand, heating to reflux afforded a rather sluggish reaction crude, from which nitroalkanol was isolated in low yields (entry 3). The complete reduction of the nitro group to an amino group requires a catalytic amount of indium in the presence of an excess (10 molar equiv) of metal. Considering that some zinc is consumed in the formation of the nitronate, an extra amount of zinc could be required for the reduction step. Accordingly, the yields are slightly better when further 5 equiv of zinc were added together with the proton source (entry 6).

Using this methodology, a 90:10 diastereomeric mixture of aminoalcohols **4a** was obtained, being the anti-isomer the major compound obtained. Under these conditions, the formation of the intermediate hydroxylamine **5a** was not observed. The anti-selectivity comes from a C–O antibonding orbital energy lowering bringing an increased stabilization of a Felkin–Anh anti-periplanar nucleophilic addition of the organoindium species to the aldehyde carbonyl group (Fig. 1).[15] The addition of aqueous acid

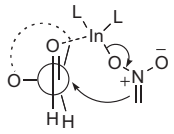
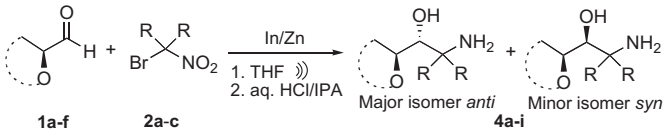


Fig. 1. Felkin–Ahn model for the attack of the indium nitronate on sugar aldehydes **1a**–**f**.

would cause, in the first instance, the formation of the nitroalcohol from the alkoxide. Then, the indium(0) in the presence of the proton source would reduce the nitro group to the corresponding amine. In the presence of zinc(0), the required indium(0) would be regenerated to continue the reduction until total conversion of the nitroalcohol into the corresponding aminoalcohol.

With the optimal conditions established, we studied the preparation of different aminosugars (Scheme 2) by reaction of sugar aldehydes **1a**–**g** with bromonitroalkanes **2a**–**c** (Fig. 2). The reaction is of general application regarding both the sugar aldehydes and the bromonitroalkanes, affording in all the cases the corresponding aminoalkanols as diastereomeric mixtures in which the anti-isomer is the major product, as predicted by the Felkin–Ahn model (Table 2).



Scheme 2. One-pot synthesis of aminoalkanols **4a**–**i** from sugar aldehydes **1a**–**f**.

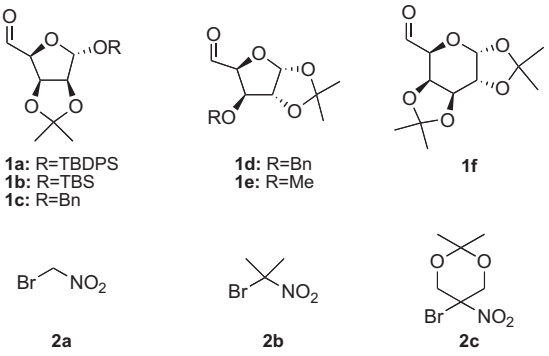


Fig. 2. Sugar aldehydes **1a**–**f** and bromonitroalkanes **2a**–**c**.

Table 2
Preparation of vicinal sugar-derived aminoalkanols **4a**–**i**

Entry	Sugar aldehyde	Bromonitro-alkane	Amino-alkanol	*anti*/*syn*[a]	Yield[b]
1	**1a**	**2b**	**4b**	100:0	52%
2	**1b**	**2c**	**4c**	100:0	54%
3	**1c**	**2a**	**4d**	78:22	61%
4	**1d**	**2b**	**4e**	85:15	49%
5	**1d**	**2c**	**4f**	76:24	51%
6	**1e**	**2a**	**4g**	69:31	62%
7	**1f**	**2a**	**4h**	87:13	64%
8	**1f**	**2c**	**4i**	100:0	52%

[a] Determined by ^1H NMR.
[b] After filtration over silica gel.

The preferential formation of the anti-isomers, as predicted by the Felkin–Ahn model, was confirmed when pure nitroalkanol **3b**[11a] was reduced by treatment with catalytic amount of indium