Tetrahedron 69 (2013) 542–550

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of glycosylamines and glyconamides using molecular iodine

Maxime B. Fusaro [a,b], Vincent Chagnault [a,b,*], Denis Postel [a,b]

[a] Laboratoire des Glucides, CNRS—FRE 3517, 10 rue Baudelocque, 80000 Amiens, France
[b] Institut de Chimie de Picardie, FR-3085, UFR des Sciences—UPJV, 33 rue Saint Leu, 80039 Amiens Cedex 1, France

ARTICLE INFO

Article history:
Received 27 September 2012
Received in revised form 31 October 2012
Accepted 6 November 2012
Available online 14 November 2012

Keywords:
Oxidative amidation
Iodine chemistry
Metal-free oxidation
Carbohydrates chemistry
Iminosugar

ABSTRACT

We describe herein the synthesis of glyconamides and glycosylamines using molecular iodine on benzylated carbohydrates. During the improvement and the optimization of the direct oxidative amidation reaction, we also discovered the possibility to form glycosylamines with excellent yields and short reaction times in comparison with the previously reported procedures. Advantages of these methods are the operational simplicity, elimination of use of complicated reagents and procedures, and generality of the reactions. Our methodology is an excellent access to precursors of *N*-alkyliminosugars and imino-*C*-glycosides.

1. Introduction

Carbohydrates are essential materials in many biological processes as they interact with proteins or enzymes.[1] They perform numerous roles in living organisms, for the storage of energy (starch, glycogen), and as structural components (cellulose, chitin). These molecules are chemically considered as polyhydroxylated aldehydes or ketones but it is possible to observe naturally occurring nitrogen containing analogs. Iminosugars, in which the endocyclic oxygen has been replaced by nitrogen, are sugar mimetics with a wide number of biological activities.[2–6] Known as glycosidase inhibitors, they also show interesting inhibitory activities over other enzymes such as glycogen phosphorylase, glycosylstransferase or metalloproteinase. Their promising therapeutic potential is illustrated, as an example, by the approval of Zavesca® (*N*-butyl-deoxynojirimycin) for the treatment of the Gaucher disease, a rare genetic disorder. Even if several hundred publications have already been published about the synthesis of iminosugars derivatives, most of these methods imply many preparation steps and lead to low overall yields.[6]

One of the most described methodologies for the synthesis of imino-*C*-glycosides goes through the preparation of glycosylamines. The hemi-aminal functional group, which can be obtained by several procedures,[7–10] can be subjected to a Grignard reaction to form an acyclic amine. The iminosugar core is then usually obtained by nucleophilic substitution or by reductive amination.[11]

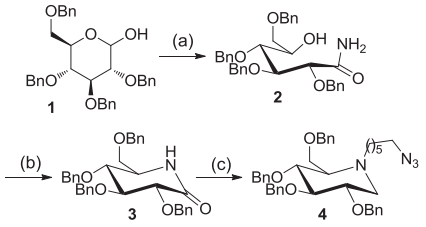
This methodology is surely one of the fastest methods leading to the formation of α-*C*-alkylated iminosugars with good overall yields. Nevertheless, in comparison with the reactivity of free carbohydrates,[12] benzylated compounds lead to longer reaction times. Five days are required for the preparation of the *N*-benzyl-2,3,4,6-tetra-*O*-benzyl-D-glucopyranosylamine but only few hours are necessary starting from the unprotected carbohydrate. Moreover, depending on the amine used, excess removal of this reagent is not always evident.

Concerning the preparation of *N*-alkyliminosugars, the poor nucleophilicity of the endocyclic nitrogen atom usually prevents the formation of these compounds in good yields using classical nucleophilic substitutions or reductive amination reactions.[13,14] Thus, numerous elegantly designed methods have been well documented in literature for their preparation but several unsolved problems still remain, for example, the large number of steps and long reaction times.[15]

More recently, a promising methodology has been published by Compain and co-workers to access to *N*-alkyliminosugars. They described the synthesis of azide-armed *N*-alkylimino-D-xylitol derivatives as key building blocks for the preparation of iminosugar click conjugates.[13,16] As shown in Scheme 1, amide **2** was obtained directly from commercially available 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose **1** in 78% yield by oxidative amidation with iodine in 30% aqueous ammonia and THF.

* Corresponding author. Tel.: +33 322828812; fax: +33 322827568; e-mail address: vincent.chagnault@u-picardie.fr (V. Chagnault).

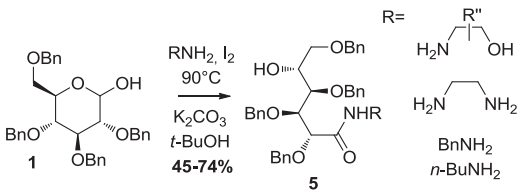
0040-4020/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2012.11.027



Scheme 1. (a) aq NH_3 (30%), I_2, THF, 16 h, 78%; (b) (i) DMSO, Ac_2O; (ii) $NaBH_3CN$, HCOOH, MeCN, 80 °C, 60% over two steps; (c) (i) LAH, THF, reflux, 90%; (ii) $Br(CH_2)_6N_3$, Et_3N, DMAP, DMF, 120 °C, 38%.

The main advantage of this metal-free reaction is that both aldehyde oxidation and C–N bond formation are performed in a single step.[17,18] The iminosugar scaffold was obtained by cyclization performed by reductive amidation and reduction of the lactam. Unfortunately, without any surprise for the reasons previously discussed, N-alkylation of the endocyclic nitrogen was obtained with only 38% yield.

To avoid this problematic N-alkylation and to reduce the number of steps, Martin and co-workers described the possibility to perform the same oxidative amidation reaction using a variety of primary amines in order to form *N*-alkylated gluconamides in one single step.[10] The reaction, performed in *t*-BuOH at 90 °C in the presence of molecular iodine, leads to modest to good yields depending on the nature of the starting materials (45–74%; Scheme 2).



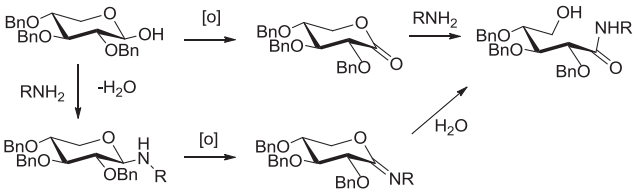
Scheme 2. Oxidative amidation described by Martin and co-workers.

Moreover, high temperature being not always compatible with volatile amines, a more adaptable methodology would be beneficial. The precise mechanism of the oxidative amidation being not well-known, it hampers optimizations and adaptations to a large variety of compounds. Being aware of the interest of such compounds and the difficulties to obtain a flexible procedure for the synthesis of glyconamides and glycosylamines on benzylated carbohydrates, we attempted to meet this challenge by optimizing and developing this oxidative amidation reaction using primary amines. We also propose another methodology for the preparation of glycosylamines.

2. Results and discussion

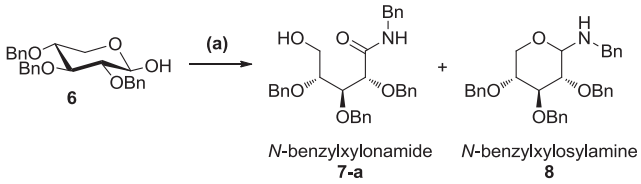
As proposed by Martin and co-workers, oxidative amidation mechanism could consist in either the oxidation of the anomeric position or the oxidation of a glycosylamine intermediate (Scheme 3).

To optimize the amidation reaction, our first approach consisted in using 2,3,4-tri-*O*-benzyl-D-xylopyranose **6**[19] (easily available at multi-gram scale) and benzylamine as model substrates. We then decided to reduce the number of parameters by carrying out our study without K_2CO_3 and by lowering the temperature. To our surprise, by varying the solvent nature we obtained very interesting results, which indicate an important solvent effect. Whatever the solvent, two different products were obtained as shown in Table 1.



Scheme 3. Oxidative amidation mechanism proposed by Martin's team.

Table 1
Solvent effect on the oxidative amidation reaction



N-benzylxylonamide **7-a** *N*-benzylxylosylamine **8**

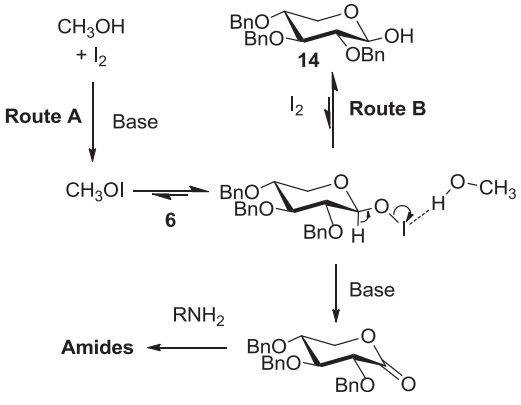
Entry	Solvent	Compound **7-a**	Compound **8**
1	CH_3CN	23%	72%
2	CH_2Cl_2	23%	67%
3	THF	30%	64%
4	*t*-BuOH	50%	45%
5	Ethanol	60%	30%
6	MeOH	*70%*	*20%*
7	MeOH[a]	70%	20%

(a) I_2, benzylamine, solvent, rt, 12 h.
[a] I_2 has been replaced by NIS.

Investigation by NMR spectroscopy indicated the presence of the desired amide and another compound containing a hemiaminal ether functional group. An *N*-benzylxylosylamine structure has been postulated and confirmed after comparison with the one observed after its synthesis using the Martin's procedure.[11]

Regarding to the results described in Table 1, the nature of the solvent seems to be determinant. At room temperature, the synthesis of compound **7-a** requires polar protic solvents whereas aprotic solvents lead to preferential formation of compound **8**. The best yield of **7-a** (70%) has been observed with methanol.

Moreover, it is interesting to note that the yield of compound **7-a** decreases when using a hindered and less acidic protic solvent as ethanol or *t*-BuOH. As shown in Scheme 4, we assume that alcohols could participate either in the formation of the *O*-iodinated species (route A) and/or in the elimination of HI (route B) through an acidic interaction. In both cases, a hindered alcohol could have difficulties in approaching the iodinated carbohydrate, which could explain the observed results in Table 1 (entry 4).



Scheme 4. Solvent effect on the oxidation process.

In order to identify the different species required for the oxidative amidation, we also tested the influence of iodonium ions using *N*-iodosuccinimide (NIS) (entry 7). Under these conditions, no differences were observed.