Carbohydrate Research 356 (2012) 163–171

Contents lists available at SciVerse ScienceDirect

Carbohydrate Research

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

I_2-mediated carbamate annulation: scope and application in the synthesis of azasugars

Bridget L. Stocker [a,*], Anna L. Win-Mason [b], Mattie S.M. Timmer [b,*]

[a] Malaghan Institute of Medical Research, PO Box 7060, Wellington, New Zealand
[b] School of Chemical and Physical Sciences, Victoria University of Wellington, PO Box 600, Wellington, New Zealand

ARTICLE INFO

Article history:
Received 13 January 2012
Received in revised form 13 March 2012
Accepted 13 March 2012
Available online 23 March 2012

Keywords:
Azasugars
Iminosugar
Carbamate
Protecting-group-free
Synthesis
Halocyclisation

ABSTRACT

The I_2-mediated carbamate annulation provides an efficient and highly stereoselective route for the synthesis of a variety of pyrrolidines and piperidines, both in the presence and absence of protecting groups. Evidence for the formation of an iodoamine intermediate during the annulation is provided and, for the first time, we explore possible mechanisms of the annulation. The high *cis*-selectivity of the carbamate annulation is also compared to other N-halocyclisations and aminomercurations and some general conclusions about the diastereoselectivity of these types of reactions are made.

1. Introduction

Azasugars, or iminosugars, are a valuable class of compounds that play an important role in drug discovery, primarily due to their ability to mimic oxocarbenium ion transition states of glycosidase reactions,[1] though other biological activities, such as their ability to act as molecular chaperones,[2] as immunomodulators,[3] or as inhibitors of other enzymes and proteins[4,5] has also been noted. Azasugars sparked scientific interest in the early 1960s with the almost simultaneous reports of the syntheses of 'piperidinoses', sugar derivatives containing a nitrogen atom in the ring, by the groups of Jones and co-worker,[6] Paulsen,[7] and Hanessian and Haskell.[8] Shortly thereafter, the first azasugar, nojirimycin (**1**) (Fig. 1), was isolated from *Streptomyces reseochromogenes* and found to possess anti-microbial activity,[9] and it's 1-deoxy analogue deoxynojirimycin (DNJ, **2**), initially prepared by Paulsen et al.,[10] was later isolated from Mulberry trees[11] and shown to be a potent α-glycosidase inhibitor.[12] The D-*gluco* chiral scaffold of the nojirimycin family has subsequently played an important role in the development of anti-diabetic drugs, such as Glyset® (**3**),[13] and represents just one of the many types of azasugars that have been isolated, synthesised and their biological activity explored in an effort to find therapeutic activities.[14,15] In addition to the aforementioned nojirimycin derivatives (**1**–**3**), which belong to the piperidine class of azasugars, other structural classes of azasugars include the pyrrolidines [e.g., 2,5-dihydroxymethyl-3,4-dihydroxypyrrolidine **4**, (DMDP, R = H)],[4,16,17] the pyrrolizidines, [e.g., casuarine (**5**)],[18] the indolizidines [e.g., swainsonine (**6**)],[19] and the nortropanes [e.g., calystegine A_3 (**7**)].[20]

Given the enormous therapeutic potential of azasugars, it is not surprising that much effort has been spent in determining efficient and novel ways to synthesise these carbohydrate-mimics, with strategies including the use of ring-closing metathesis, reductive amination, aldol reactions and pericyclic reactions.[15] Our interest, however, was in developing a carbamate annulation, which, in addition to providing the chemist with an additional 'synthetic tool', would allow for the synthesis of azasugars without the need for protecting groups.[21] It goes without question that the use of protecting groups adds to the total number of steps in a synthetic sequence and leads to reduced overall efficiencies,[22] and because of this, 'protecting-group-free' methodology has received much attention in recent years.[23] That said, it can often be difficult to design or implement a protecting-group-free synthesis due to the competing 'reactive' centres around a molecule. Accordingly, we became interested in determining the versatility of our carbamate annulation for the synthesis of azasugars, both in the presence and absence of protecting groups. This mini-review highlights this work and outlines the scope and limitations of our carbamate annulation for the synthesis of pyrrolidine and piperidines, and also explores how this annulation relates to similar electrophilic cyclisations.

* Corresponding authors. Tel.: +64 4 499 6914x813; fax: +64 4 499 6915.
E-mail addresses: bstocker@malaghan.org.nz (B.L. Stocker), mattie.timmer@vuw.ac.nz (M.S.M. Timmer).

0008-6215/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.carres.2012.03.015

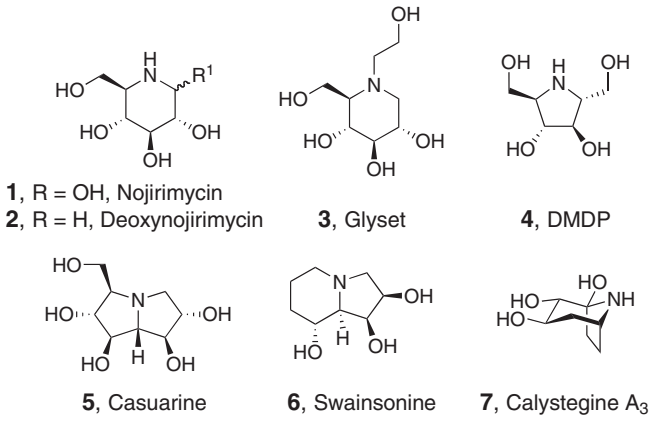
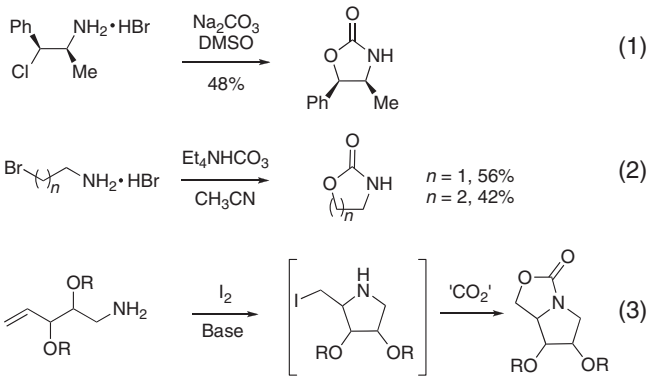


Figure 1. Representative azasugars.



Scheme 1. The potential of 1,2-haloamines in the synthesis of carbamates.

2. Carbamate annulation: synthesis of pyrrolidines and piperidines

Organic carbamates have found wide application in chemistry with their use as pharmaceuticals and pharmaceutical intermediates, as agrochemicals, as linkers in combinatorial chemistry, and as protecting-groups during peptide couplings.[24] It is thus not surprising that a number of strategies have been developed for the synthesis of carbamates and these include the reaction of amines with phosgene (or derivatives), carbon dioxide (gaseous, electrochemical and supercritical), carbonate esters and salts, or the use of amides in, for example, Hoffmann, Curtius and Lossen rearrangements.[24] In particular, we became interested in the seminal work by Hassner and Burke[25] and Inesi et al.[26] who illustrated that cyclic carbamates could be prepared, in modest yield, from the reaction of acyclic amines equipped with a halogen-leaving group and either sodium carbonate or tetraethylammonium bicarbonate, respectively (Eqs. 1 and 2, Scheme 1). Tamaru et al. have also used sodium bicarbonate and iodine in the halocyclisation of preformed olefinic carbamates (methoxycarbonyl amides), but cyclisation of these substrates was slow and poor-yielding and often led to mixtures of five- and six-membered cyclic amides.[27] Notwithstanding much optimisation, we thus saw the potential of extending this type of halocyclisation to allow for the synthesis of carbamates from unprotected alkenylamines in a one-pot process, whereby the intermediate halide would be formed in situ and subsequently cyclised in the presence of 'CO_2' (Eq. 3; Scheme 1). The annulation, in turn, would form an integral part of our strategy for the synthesis of azasugars.

To examine the potential of a carbamate annulation in the synthesis of azasugars, we envisioned a retrosynthetic strategy whereby the target compounds **A** could be readily prepared from the precursor carbamates **B** via base-mediated hydrolysis (Scheme 2). Carbamates **B**, in turn, could be formed via our proposed I_2-mediated annulation, with the pre-requisite alkenylamines **C** being prepared from the parent sugars **D** via a Vasella reaction[28] and either a reductive amination[29] or a Strecker reaction.[30] In this manner, five-membered azasugars (e.g., $n = 2$, $R^1 = H$ or $R^1 = CH_2NH_2$) and six-membered azasugars (e.g., $n = 3$, $R^1 = H$) could be readily prepared.

With this general approach in mind, we first considered the potential of our carbamate annulation in the protecting-group-free synthesis of pyrrolidines (Scheme 3).[21,31,32] Here, the parent pentose **8** was readily converted into the corresponding alkenylamine **9** via a Vasella reaction followed by our protecting-group-free reductive amination,[29] and then subjected to a solution of I_2 and various saturated carbonates in H_2O. While there is much precedent for the formation of iodomethylpyrrolidines when treating pentenylamines with I_2 and molar equivalents of $NaHCO_3$,[33,34] we were delighted to observe that the desired carbamate **10** could be formed in one step and excellent yield and diastereoselectivity when excess $NaHCO_3$ was used.[21] The carbamate annulation favours formation of the 2,3-*cis* pyrrolidine (d.s. > 20:1, as evidenced by ^1H NMR of the crude reaction mixture), with the stereochemistry at the 3-position exerting stereocontrol over the cyclisation. Using this strategy, a variety of carbamates were prepared, including those derived from 2-deoxy-D-ribose ($R^1 = H$),[31] and these were subsequently treated with NaOH in refluxing EtOH to give the desired pyrrolidines **11** [1,4-dideoxy-1,4-imino-L-xylitol,[32] 1,4-dideoxy-1,4-imino-D-lyxitol,[32] 1,4-dideoxy-1,4-imino-D-xylitol,[21] 1,4-dideoxy-1,4-imino-L-lyxitol[21] and 1,2,4-trideoxy-1,4-imino-L-xylitol[31]] in excellent (48–57%) overall yields.

Having illustrated the application of the carbamate annulation for the synthesis of hydroxy-pyrrolidines, we then explored the potential of this methodology in the synthesis of aminoiminohexitols, which in turn have shown great promise in the treatment or diagnosis of numerous diseases including osteoarthritis,[35,36] bacterial infection,[37] and lysosomal storage disorders.[38,39] We initially envisioned another protecting-group-free synthesis, whereby the unprotected methyl 5-deoxy-5-iodo-D-arabinoside (**12**, $R^1 = H$) could be transformed into α-aminonitrile **13** via a Vasella reaction and subsequent Strecker condensation, however, under all conditions attempted, at best, only minor amounts (<5%) of the desired α-aminonitrile could be isolated and significant product degradation was observed (Scheme 4).[40] Though disappointing, hydroxyaldehydes are well known to be prone to decomposition,[41] so we turned our attention to the use of a protected furanoside as a starting substrate, confident that our cabamate annulation methodology would still allow for a competitive synthetic route. To this end, protected arabinoside **12** (R^1 = Bn) was subjected to a Vasella reaction and the corresponding aldehyde was formed in excellent (97%) yield. After optimisation, it was found that a good (88%) yield and diastereoselectivity (9:1; *syn:anti*) for the Strecker reaction could be obtained when TMSCN was used as the source of nitrile and NH_4OAc as the source of amine, with a Cram-chelate transition state explaining the preferred *syn* stereoselectivity.[40]

The α-aminonitriles were readily separated by flash column chromatography and the major diastereomer (*syn*-**13**) was treated with a solution of I_2 and $NaHCO_3$ (satd) in a mixed solvent system (THF/H_2O, 1:1) to solubilise the lipophilic α-aminonitrile while allowing for sufficient dissolution of $NaHCO_3$. We were unsure whether our carbamate annulation would occur in a mixed solvent system, and moreover, whether we would generate the primary iodide, as suggested by the literature.[33,34,42] We were therefore delighted to observe the smooth transformation of *syn*-**13** into carbamate **14** (85% yield), thus highlighting the potential of our methodology during more conventional organic syntheses. As with the