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Cycloaddition reactions of sugar-based olefins, nitrones and nitrile oxides. En route to saccharidic spiroisoxazoli(di)nes

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Isoxazoline and isoxazolidine-containing compounds are privileged structures of interest, notably in synthetic and medicinal chemistry. These heterocycles can be obtained by 1,3-dipolar cycloaddition reactions between an olefin and a nitrile oxide or a nitrone. This reaction generates the formation of one C-C and one C-O bond and up to three chiral centers in one step. In the present chapter, we aim to summarize and discuss reports of these cycloadditions on sugar olefins, with a focus on *exo*-methylene sugars or activated *exo*-glycals, leading with high regio- and stereocontrol to saccharidic spiroisoxazoli(di)nes. Additional examples of cycloaddition reactions involving chiral nitrone, sugar nitrile oxide, sugar nitrone and also two chiral sugar partners will also be discussed. Due to the importance of the spiro structure in several biologically active compounds, these spiroheterocycles can be regarded as spironucleoside analogues, mimics of natural building blocks or multicyclic sugar scaffolds suitable for selective derivatization. Some of them thus showed promising biological properties as antibacterial agents or enzyme inhibitors. Moreover, the labile nature of the N−O bond in the isoxazolidine ring makes it an attractive target for synthetic chemists. The reactivity of this scaffold has therefore been widely studied and the cycloadducts have been converted to other classes of compounds of interest. Examples of the biological relevance and synthetic use and reactivity of these spiro-sugars will be given in this chapter.

1. Introduction

The five-membered heterocycle isoxazolidine is part of several natural products and can be a useful synthetic intermediate due to the labile nature of the N−O bond. As reported in an excellent review from I. Parrot and J. Martinez, [1] these compounds can be considered as natural building blocks analogues, *i.e.* nucleosides and carbohydrates analogues and can also be incorporated into peptidic sequences for the design of peptidomimetics. From a medicinal point of view, these derivatives provided many biological applications as cytotoxic, antiviral or antimicrobial compounds. These heterocycles are commonly obtained through the well-known 1,3-dipolar cycloaddition between an olefin and a nitrone thus generating the formation of one C-C and one C-O bond [2–6].

Isoxazoline derivatives, the unsaturated parent of the five-membered heterocycle isoxazolidine, are also a class of heterocyclic compounds of significance, since they are frequently found in many compounds that showed significant biological activities [7]. Besides, they can be easily transformed into other functional groups, making them valuable compounds in synthetic chemistry. Nitrile oxide cycloaddition with olefin represents an easy route to this type of heterocycle [8, 9].

Reactivity of carbohydrate-derived olefins has been tested in this type of cycloadditions [10–13]. In the present chapter, we aim to summarize and discuss reports of these cycloadditions

on sugar olefins, with a focus on *exo*-methylene sugars or activated *exo*-glycals, leading with high regio- and stereocontrol to saccharidic spiro-isoxazoli(di)nes. *Exo*-glycals or *C*-glycosylidenes have an exocyclic double bond at the anomeric center [14, 15]. These compounds can be efficiently prepared by various olefination processes starting from sugar lactones and taking advantage of Wittig-type olefination or other organometallic reagents.

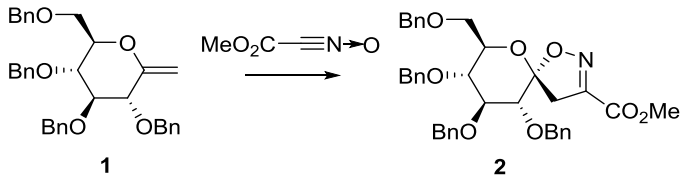
The first part of the present chapter is dedicated to *exo*-methylene sugars (anomeric and non-anomeric) as dipolarophiles in cycloaddition reaction with nitrile oxide and nitrone. We then focus on *exo*-glycals substituted by an electro-withdrawing group, labelled "activated *exo*-glycals" and widely studied in our group with regard to their singular reactivity. Finally, the last part of this chapter describes some representative examples of 1,3-dipolar cycloaddition reactions of carbohydrate derived nitrones and nitrile oxides.

2. *Exo*-methylene sugars as dipolarophiles

In this first part, we report 1,3-dipolar cycloadditions with anomeric and non-anomeric *exo*-methylene sugars or activated *exo*-glycals as dipolarophile partners.

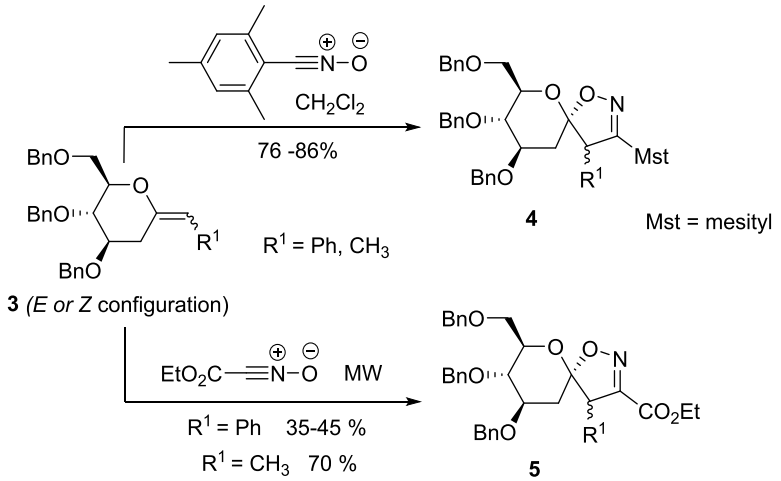
2.1. Anomeric *exo*-methylene sugars as dipolarophiles

RajanBabu *et al.* described the first example of 1,3-dipolar cycloaddition of methylene *exo*-glycals with nitrile oxide [16]. The tetrabenzyl protected derivative **1** efficiently reacted with carbomethoxynitrile oxide to stereospecifically give spiro-isoxazoline **2**, considering steric hindrance on β face (Scheme 1).



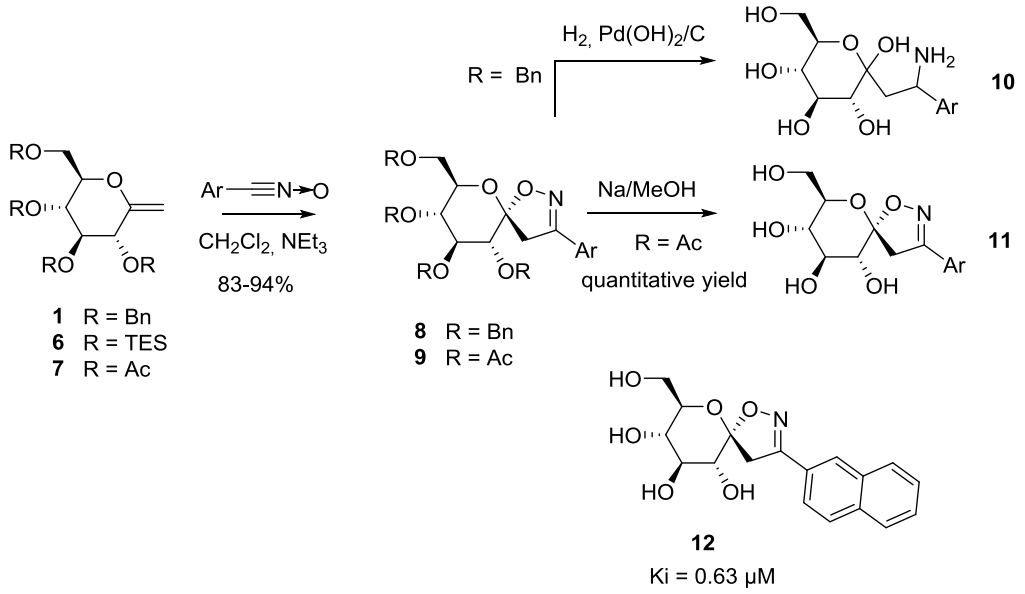
Scheme 1. Synthesis of the first saccharidic spiro-isoxazoline described by RajanBabu

Few years later, Lieberknecht and Bravo gave full experimental accounts of this reaction and applied it to *Z*- or *E*- configurated *exo*cyclic enolethers **3** (Scheme 2) [17]. Starting from the *E*-configurated olefin, the cycloaddition reactions were performed with mesitonitrile oxide (stable monomer) in dichloromethane and *trans*-configurated cycloadducts **4** were obtained in excellent yields. With ethoxycarbonylnitrile oxide generated *in situ*, microwave irradiations were the most efficient for the cycloaddition on these trisubstituted alkenes **3**, in particular for the less reactive 1-phenylenitol (R^1 = Ph). The diastereoisomeric ratio determined by NMR experiments confirmed the proposed structures for compounds **4** and **5**, in agreement with the attack of the nitrile oxide to the less hindered face of the *exo*-glycal. Starting from *E*-configurated *exo*-glycals, the *trans* cycloadducts were mainly obtained (95:5) and the *cis* configurated cycloadducts were the main compounds when the reaction was performed on the *Z*-isomers. The regioselectivity was in line with trends found in nitrile oxide cycloadditions to trisubstituted alkenes [4].



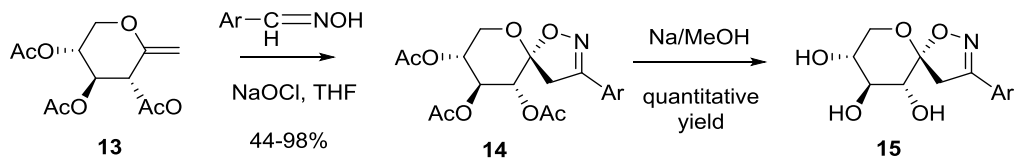
Scheme 2. Cycloadditions on *Z*- or *E*-configurated *exo*cyclic enolethers

As part of their project concerning glucose derivatives as glycogen phosphorylase (GP) inhibitors, Praly *et al.* deeply developed the 1,3-dipolar cycloaddition of various aryl nitrile oxides to differently protected *exo*-glucals (Scheme 3) [18]. They demonstrated that the benzylated *exo*-glucal **1** afforded the corresponding spiro-isoxazoline **8** in high yields (83-94%) with complete regio- and stereoselectivity established by 1D, 2D and NOESY NMR experiments. However, the reductive cleavage of the N–O bond during hydrogenolysis of benzyl protecting group prompted them to envisage another hydroxyl protecting group like the triethylsilyl group (TES). On derivative **6**, the cycloaddition of the aryl nitrile oxide did not give the expected cycloadduct. Finally, the acetylated methylene *exo*-glucal **7** was efficiently transformed in the corresponding adduct **9** subsequently deprotected by methanolysis. The obtained water-soluble spiro-isoxazolines were evaluated as glycogen phosphorylase inhibitors and showed IC_{50} values in the micromolar range. The X-ray structures of the enzyme-ligand complexes showed that this new family of glucose-based spiro-isoxazolines preferentially binds at the catalytic site of the enzyme retaining the less active T-state conformation [19]. Compound **12**, prepared by this methodology, presented the best biological activity with a Ki value of 0.63 µM for inhibition of GPb and was therefore deconstructed and used in an fragment-based binding evaluation [20]. Furthermore, 2-naphthyl substituted glucopyranosylidene-spiroisoxazoline **12** was selected for further *in vitro* and *in vivo* evaluation on a rat model (Zucker fa/fa model) and the promising results indicated that this type of compounds can be considered as anti-hyperglycemic agents in the context of type 2 diabetes treatment [21].



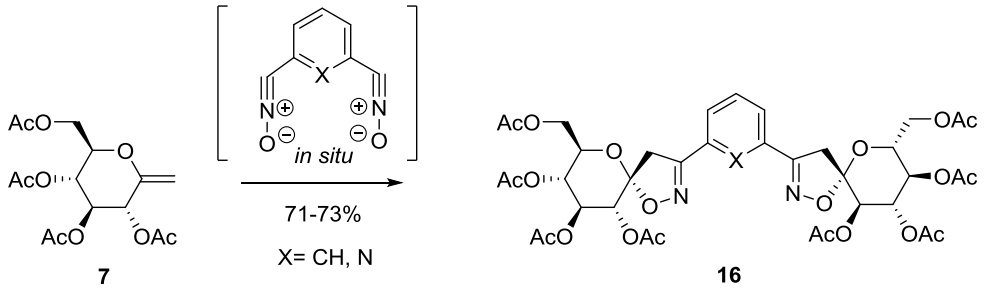
Scheme 3. Water-soluble spiro-isoxazolines as GP inhibitors

More recently, new spiro-isoxazolines from D-xylose were synthesized by cycloaddition of *O*-peracetylated *exo*-xylal **13** with various nitrile oxides prepared *in situ* by oxidation of the corresponding aromatic aldoximes **14** (Scheme 4) [22]. Here again, the configuration of the anomeric spiro-carbon was determined by NOE and similar stereoselectivities were observed in the formation of glucose- and xylose derived spiro-isoxazolines. The fully deprotected compounds **15** were evaluated toward GPb inhibition and showed moderate activity, highlighting the importance of the glucose moiety.



Scheme 4. Xylose derived spiro-isoxazolines

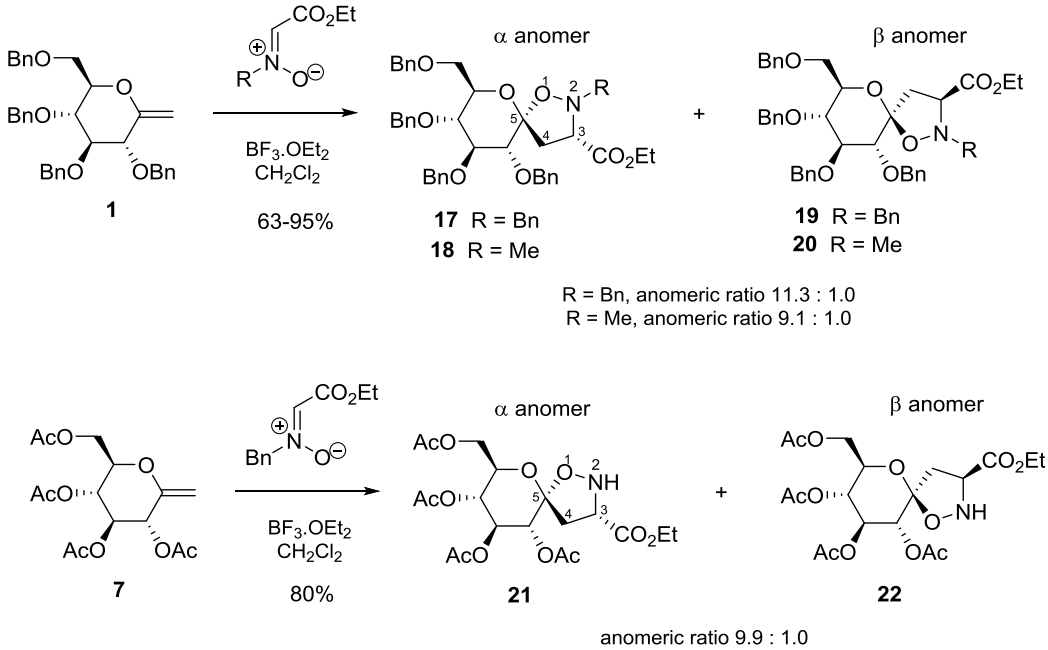
In the field of asymmetric catalysis, carbohydrates are excellent starting materials for the preparation of chiral auxiliaries. In this context, Vidal *et al.* efficiently used 1,3-dipolar cycloaddition of a bis(nitrile oxide) and methylene *exo*-glucal for the preparation of carbohydrate-based bis spiro-isoxazoline ligands like **16** (Scheme 5) [23]. These ligands were evaluated in a Pd-catalyzed Tsuji–Trost reaction but did not provide good results. Ring opening and formation of isoxazole, detected in the reaction mixture after addiction of Pd(II), probably explain the low yields. The carbohydrate-based bis spiro-isoxazoline ligands were also evaluated in Cu(I)-catalyzed asymmetric imine alkynylation and, in this case, the addiction products were obtained in good yields.



Scheme 5. Carbohydrate-based bis spiro-isoxazolines as ligands for asymmetric catalysis

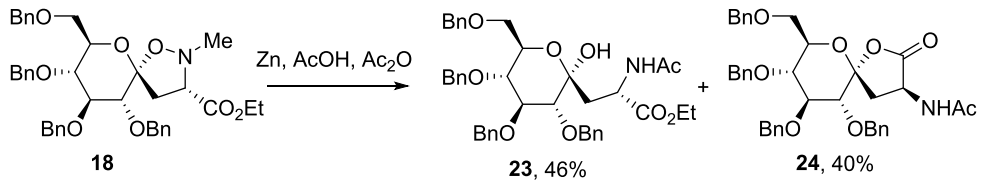
1,3-Dipolar cycloaddition of nitrones with alkenes is widely used in organic synthesis and Ikegami *et al.* described this reaction on 1-methylenesugar **1** under $BF_3.Et_2O$ catalysis. At low temperature, the cyclization took place in a diastereoselective manner and afforded in good to excellent yields the corresponding spiro-isoxazolidines (Scheme 6) [24, 25]. The yields and the reaction stereoselectivities were slightly affected by the nature of the solvent, the temperature, the number of equivalents of catalyst and the steric hindrance of the nitrone. Although four diastereomers can be potentially obtained (two anomeric isomers with R and S configuration on C-3), only two anomeric isomers **17** and **19** or **18** and **20** with R-configuration on C-3 were obtained, with α-isomers **17** and **18** as the predominant compounds.

The 1,3-dipolar cycloaddition reactions were also performed on manno- and galacto-benzylprotected *exo*-glycals and similar results were obtained. Concerning mannose derivative bearing an axial benzyloxy group on position 2, an increase of β-stereoselectivity was observed (α:β ratio, 5.4:1 to 1.9:1 depending on experimental conditions and on the nitrone substitution). In the same manner, the 1,3-dipolar cycloaddition on the acetyl-protected 1-methylenesugar **7** was also performed under $BF_3.OEt_2$ catalysis and similar results were obtained.



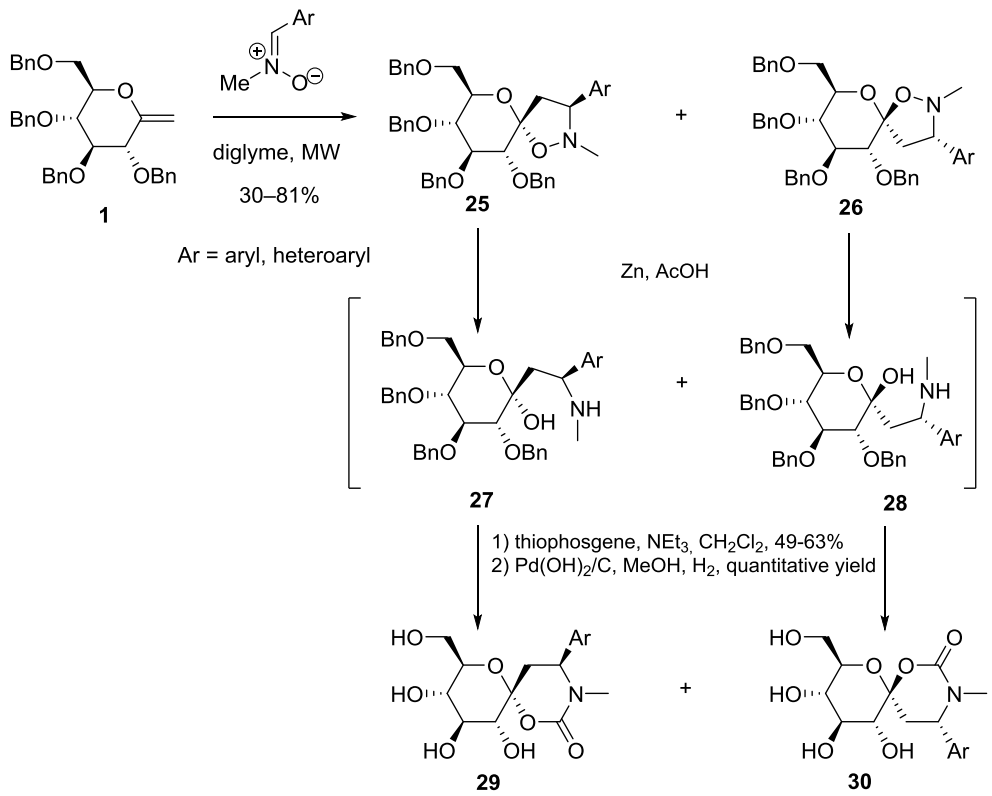
Scheme 6. Synthesis of spiro-oxazolidines by $BF_3.Et_2O$ catalysis

Interested by the development of glycosyl amino acids, Ikegami *et al.* described a new access to *C*-glycosyl amino acids from spiro-isoxazolidines by reductive cleavage of the N-O bond (Scheme 7). The treatment of spiro-isoxazolidine **18** with Zn in acetic acid and acetic anhydride solution resulted in the formation of *C*-glycosyl amino acid **23** with retention of configuration at C3. Compound **24** resulting from intramolecular lactonization was also obtained.



Scheme 7. Access to *C*-glycosyl amino acid by cleavage of N-O bond

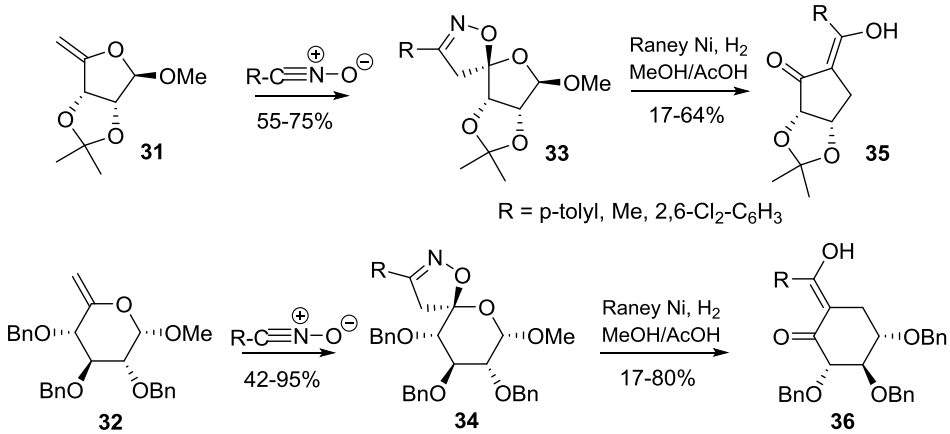
This efficient approach was employed by Li *et al.* for the preparation of novel spiro-isoxazolidines by 1,3-dipolar cycloaddition with various nitrones [26]. Amino-*C*-glycosides **27** and **28** obtained as an anomeric mixture were sometimes difficult to separate because of their similar polarities (Scheme 8). Nevertheless, these compounds were useful intermediates for the preparation of oxazinanone derivatives containing sugar moiety and obtained by cyclization with triphosgene. As spironucleosides analogues, the biological activities against glycosidases and cytotoxicities of deprotected compounds **29** and **30** were evaluated and two derivatives showed selective inhibition properties against β-glucosidase and a slight antitumor activity.



Scheme 8. Preparation of oxazinanone derivatives containing a sugar moiety

2.2. Others *exo*-methylene sugars as dipolarophiles

Carbohydrates are useful building blocks for the preparation of highly functionalized cyclopentane and cyclohexane rings found in biologically interesting compounds. In this context, Gallos *et al*. described the elegant synthesis of carbocycles **35** and **36** starting from hex-5-enopyranoside and pent-4-enofuranoside (Scheme 9) [27–29]. Cycloadditions of nitrile oxides with *exo*-glycals **31** and **32** respectively gave spiro-isoxazolines **33** and **34** in good yields. These compounds were efficiently transformed into the corresponding carbocycles by action of Ni Raney in a mixture of methanol and acetic acid. Functionalized carbocycles **35** and **36** were obtained by reductive opening of the heterocyclic ring and spontaneous intramolecular aldol-like condensation. The hydroxylated six- and five-membered cyclic enaminones were the main products of the reaction but the authors reported that by-products could be formed in some cases depending on the reaction conditions, the nature of substituents and the ring size.

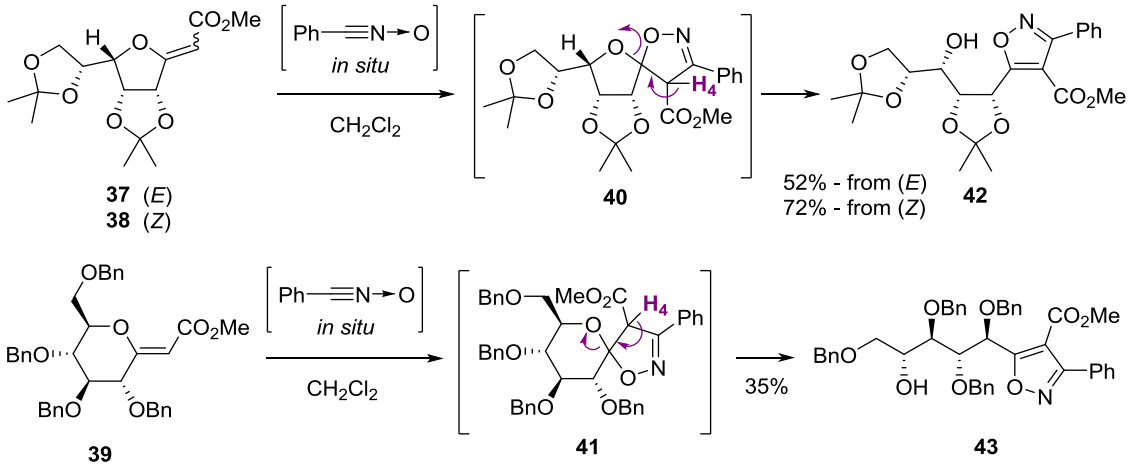


Scheme 9. Spiro-isoxazolines as intermediates for the synthesis of functionalized carbocycles

2.3. Activated *exo*-glycals as dipolarophiles

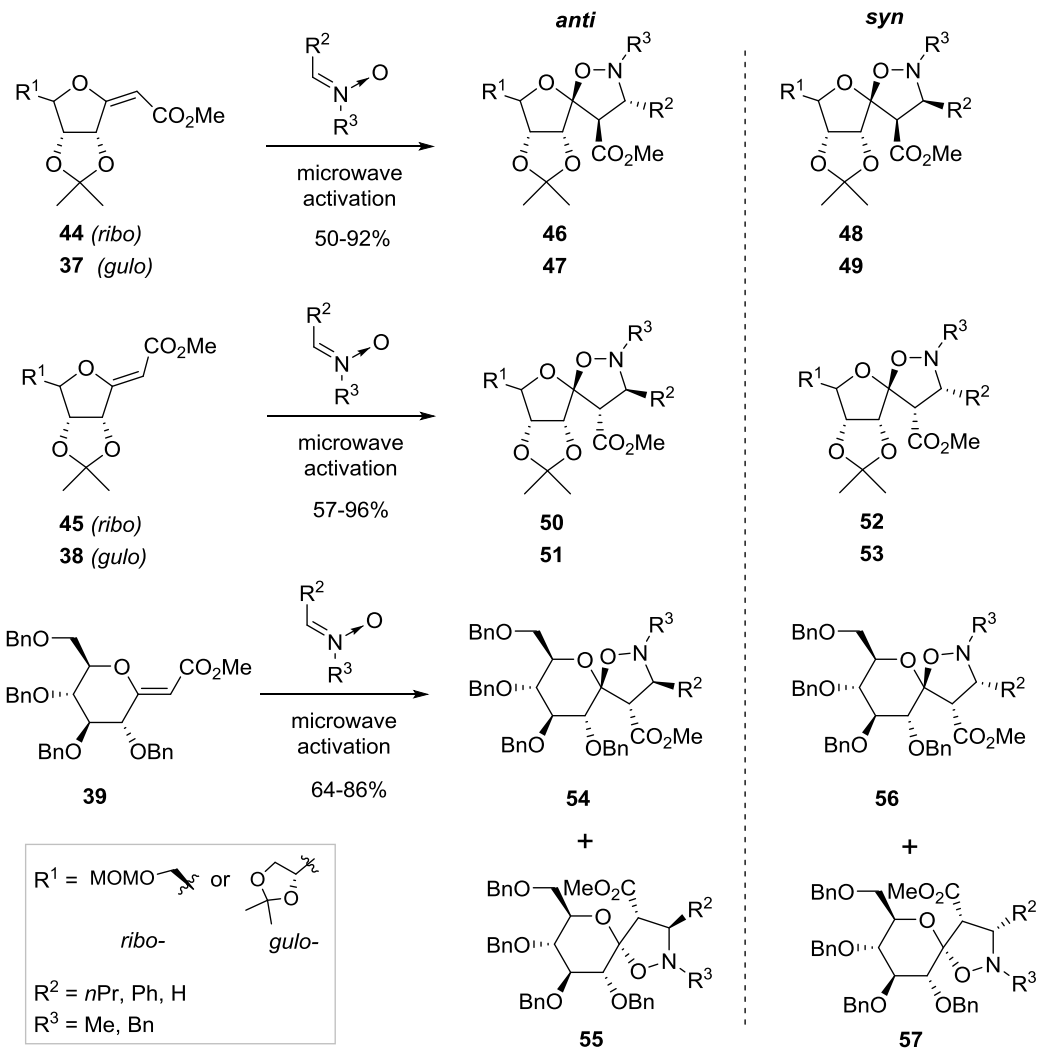
Unsaturated sugar olefins labelled “activated” possess an exocyclic double bond substituted by an electro-withdrawing group, giving them a capto-dative structure and a singular reactivity. Our group, headed by Yves Chapleur until 2014, developed a high-yielding, one-step method to prepare a series of activated *exo*-glycals. The saccharidic olefins were obtained in excellent yields as an easily separable mixture of *Z* and *E* isomers, *via* Wittig reaction on sugar lactones [14, 30]. We investigated their behaviour in cycloaddition reactions with nitrile oxides and nitrones several years ago and we recently explored the potential biological activities of spiro-isoxazolidines based carbohydrates.

Cycloaddition of activated *exo*-glycals **37**, **38** and **39** was firstly tested with benzonitrile oxide (Scheme 10) [31, 32]. Reaction proceeded smoothly at room temperature but the expected spiro-isoxazolines **40** and **41** were not obtained and careful NMR examination indicated formation of open-chain compounds **42** and **43** in 52 or 72 and 35% yields respectively. Indeed, due to the basic conditions needed for *in situ* nitrile oxide formation, abstraction of acidic proton H_4 promotes the aromatization into the corresponding isoxazoles *via* β-elimination of the sugar ring oxygen. Jimenez *et al.* had previously observed such rearrangement of activated olefins when reacted with nitrile oxides [33].



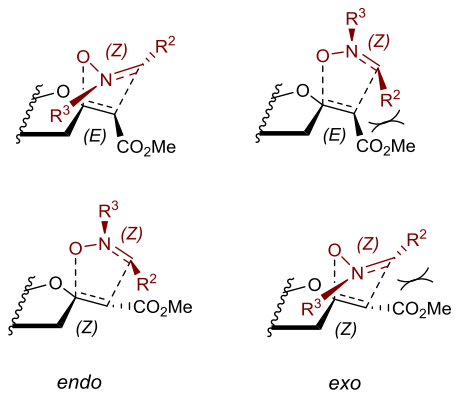
Scheme 10. Cycloadditions of activated pyrano- and furano-*exo* glycals with nitrile oxide

In similar fashion, the reactivity of these activated sugar olefins towards cycloaddition with nitrones was also explored in our group (Scheme 11). It is noteworthy that these reactions exclusively proceeded under microwave activation, no reaction occurring in standard thermal conditions. Cycloadducts were obtained in average to excellent yields depending on sugar and double bond configuration or nitrone substitution. On furano-*E*-*exo*-glycals **37** and **44**, cycloaddition with unsubstituted nitrone (R^2 = H) generated only one diastereoisomer, implying a complete facial control due to the stereochemistry of the sugar moiety and the steric hindrance on α face. When considering more substituted nitrones ($R^2 \neq$ H), two diastereoisomers at C3 where obtained, *anti* compounds **46** and **47** being the major ones as expected. However, the *anti*/*syn* ratio was also dependant on the nature of R^3 substituent. Indeed, bulky substituents like benzyl group gave a 1:1 ratio, whereas a small substituent like a methyl group led to a 4:1 *anti*/*syn* ratio in the case of **37** (*gulo* derivative). Similar results were obtained on furano-*Z*-*exo*-glycals **38** and **45**, except that *anti* selectivity was greatly enhanced with *ribo* olefin **45**. However, when considering pyrano-*exo*-glycal **39**, a different behaviour was observed. Cycloaddition with unsubstituted nitrone (R^2 = H) led to both anomers and four adducts **54-57** were obtained in case of reaction with substituted nitrones ($R^2 \neq$ H), indicating an overall poor facial selectivity of the sugar ring.



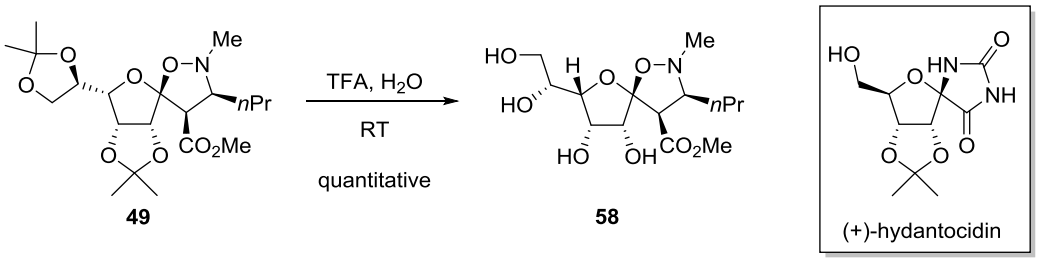
Scheme 11. Cycloadditions of activated pyrano- and furano- *exo*-glycals with nitrones

The stereochemistry of the cycloadducts and the *anti*/*syn* ratios were rationalized through postulated transition states (TS, Scheme 12). In *endo* TS case, steric hindrance between methyl ester and R^2 group is minimized for both *E* and *Z* *exo*-glycals, whereas *exo* TS is congested and formation of corresponding *syn* compounds is therefore disfavoured.



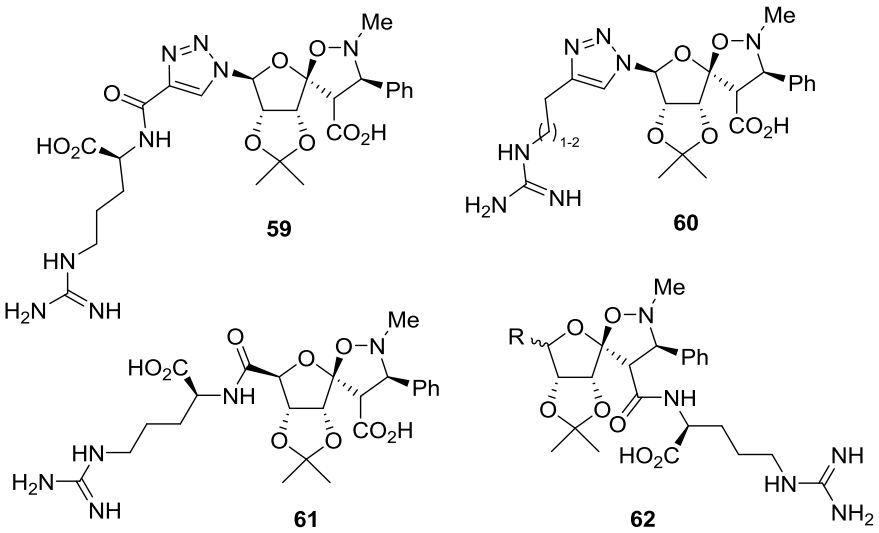
Scheme 12. Postulated transition states

These spiro-isoxazolidines, easily deprotected in acidic media, can be considered as spironucleoside analogues and have thus potential biological properties. Indeed, the natural spironucleoside (+)-Hydantocidin displays both a plant growth regulatory function and a potent herbicidal activity harmless to microorganisms and mammals [34]. As an example, the deprotection of representative spiro-saccharide **49** was carried out with trifluoroacetic acid in water, giving **58** in quantitative yield (Scheme 13). It was established that these compounds are stable in acidic conditions and do not undergo furano to pyrano isomerization and that anomeric configuration is maintained through deprotection.



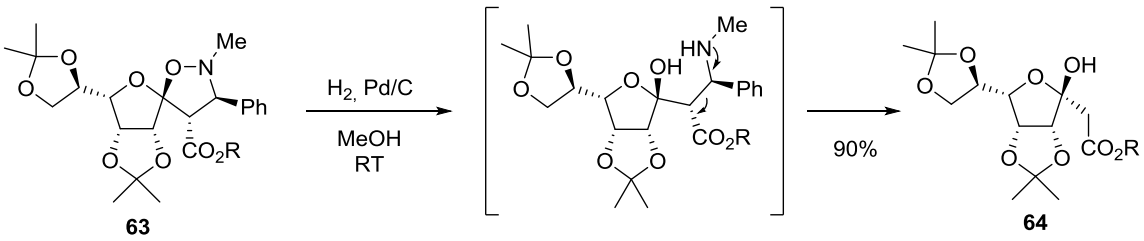
Scheme 13. Acidic deprotection of spiro-isoxazolines

To explore the potential biological activities of spiro-isoxazolidines based carbohydrates, we prepared a library of peptidomimetics for Neuropilin-1 (NRP-1) targeting (Scheme 14) [35]. NRP-1 is a transmembrane receptor of VEGFR-A implicated in various biological processes and notably angiogenesis. Our group has been interested in NRP-1 targeting for a few years with the aim of building a sugar-based peptidomimetic of the natural ligand of NRP-1 [36]. Using a sugar as a template provides a selected chirality and enables a precise spatial orientation of the substituents. In this context, we opted for a saccharidic spiro-isoxazolidine template presenting several anchoring points. Following previous studies on NRP-1/VEGFR-A interactions, we functionalized the spiro scaffolds at two sites with arginine or arginine-like groups via copper azide alkyne catalysed reaction (compounds **59** and **60**) or peptidic coupling (**61** and **62**) and tested their binding properties. However, given the moderate affinity of these peptidomimetics for NRP-1, the central bicyclic structure was probably too bulky for an appropriate binding to the receptor. Molecular modelling studies corroborated this hypothesis and helped us design more appropriate ligands [37, 38].



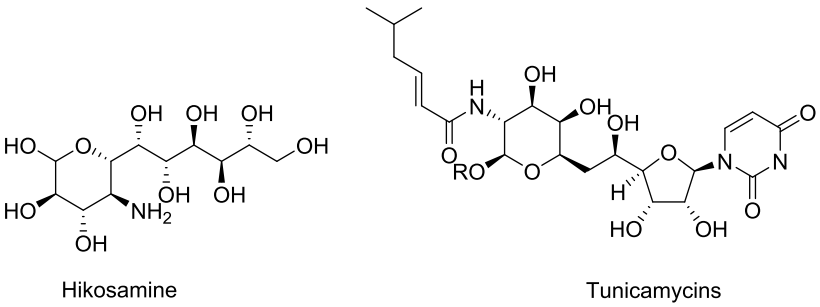
Scheme 14. Spiro-isoxazolidine based peptidomimetics for NRP-1 targeting

The labile nature of isoxazolidine N-O bond makes it a valuable target for synthetic chemists and, as described by Li *et al.* [26, 39] and Gallos *et al.* [29], it can be easily cleaved with Zn in acetic acid and acetic anhydride or in Raney nickel hydrogenation conditions (cf I.1. above). During our work related to synthesis of NRP-1 peptidomimetics, we noted a similar cleavage of the N-O bond during hydrogenolysis of **63**, leading to isoxazolidine ring opening and loss of N-benzylmethyl amine moiety (Scheme 15).



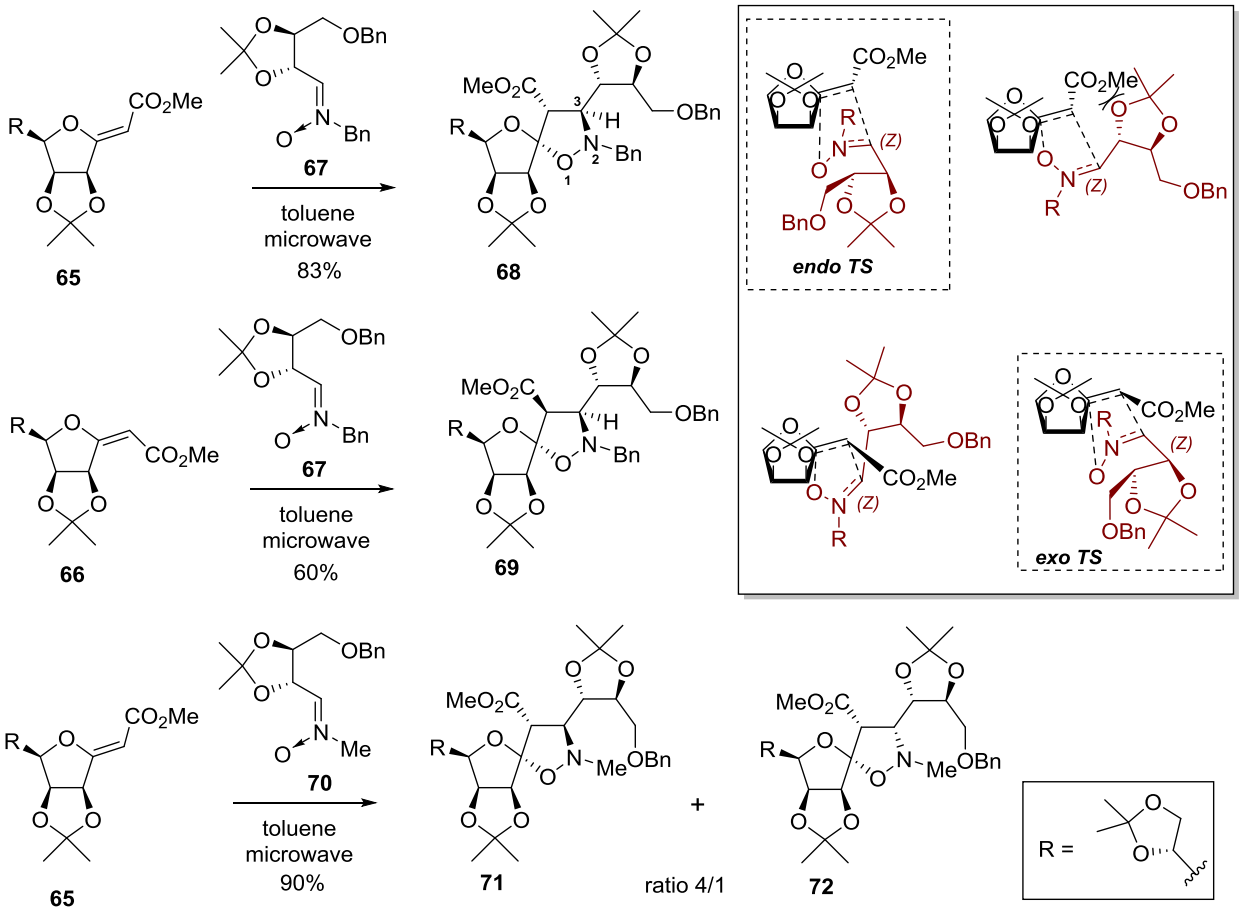
Scheme 15. Isoxazolidine cleavage by hydrogenolysis

Very few examples are reported on cycloadditions reactions between two sugar partners, although this reaction could lead to highly chiral analogues of natural products like hikosamine or tunicamycins (Scheme 16) [40]. Indeed, this synthetic approach would benefit of the easiness of isoxazolidine ring opening combined to the facial selectivity and chirality of the sugar moieties.



Scheme 16. Long chain sugars natural products

In this context, we more recently examined the cycloaddition of activated *exo*-glycals with carbohydrate-derived nitrones (Scheme 17). Nitrones were beforehand prepared by Swern oxidation of protected L-threitol followed by reaction with appropriate hydroxylamines. Then, starting from mannose olefins **65** or **66**, cycloaddition with nitrone **67** led to a single product in both cases, **68** and **69** respectively. This indicates an excellent facial selectivity induced by steric hindrance on β face of *exo*-glycals. Moreover, due to the bulkiness of benzyl group on nitrone **67**, only one C-3 diastereoisomer was obtained. Configurations at C-3/C-4 were established from the coupling constants between protons H-4 and H-3 and indicated an *anti* configuration for adduct **68** and a *syn* configuration for **69**. These observations may be rationalized by analysis of postulated transition states. In the case of *Z-exo*-glycal, *endo* TS minimizes the steric hindrance, leading to compound **68** exclusively. For *E-exo*-glycal **66**, interactions of the nitrone benzyl group with the sugar ring destabilizes the *endo* transition state and formation of **69** probably arose from an *exo* TS. When performed with less hindered nitrone **70** on *exo*-glycal **65**, the same reaction led to the formation of two C-3 diastereoisomers **71** and **72** in excellent yield, compound **71** (*anti* configuration) being the major product.



Scheme 17. Cycloadditions with open-chain sugar olefins.

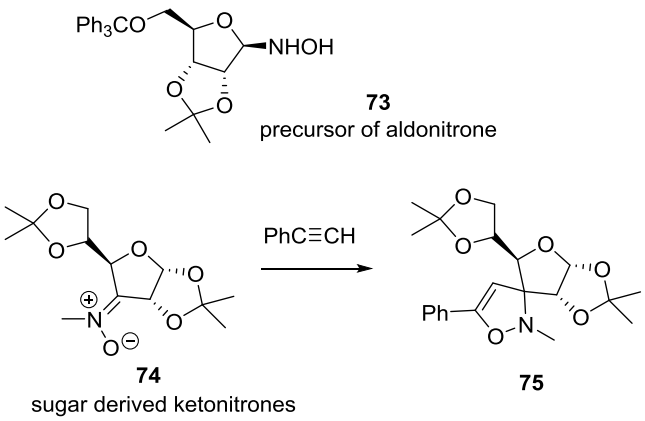
As seen in these examples, cycloaddition between carbohydrate based nitrones and enoates is a valuable way to connect two sugars *via* generation of three new chiral centers, leading to complex carbohydrates and up to nine chiral centers. The remarkable selectivity of sugar-based nitrones has been explored on cycloaddition reactions with various olefins and the last part of this chapter focuses on some representative examples.

3. Carbohydrate derived nitrones and oximes as 1,3-dipole

This part is dedicated to sugar-based nitrones and nitrile oxides involved in cycloaddition reactions with various olefins and leading to saccharidic spiroisoxazolines and spiroisoxazolidines.

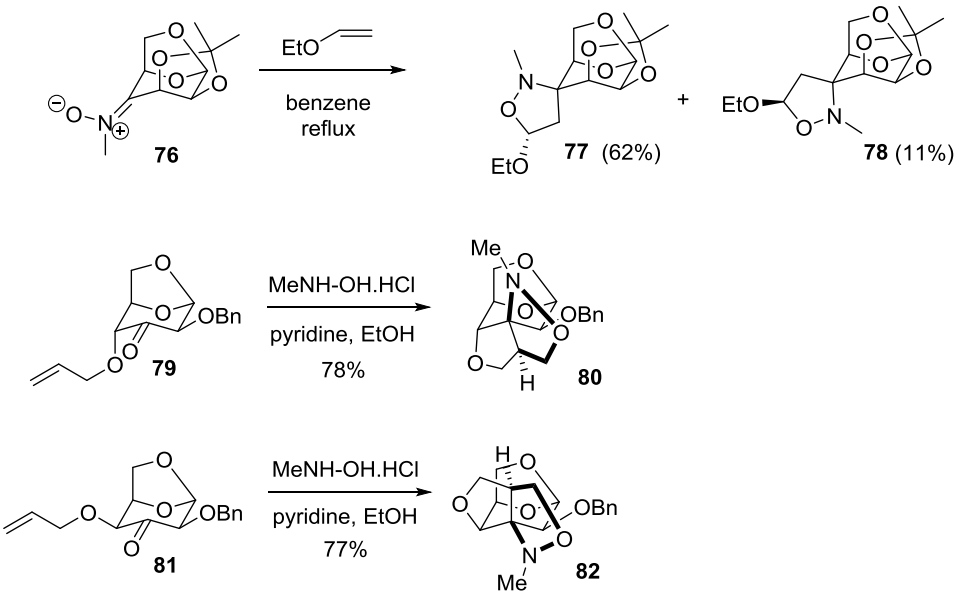
3.1. Non-anomeric sugar nitrones or nitrile oxides

The 1,3-dipolar cycloaddition of aldonitrones [8] and in particular sugar derived aldonitrones prepared *in situ* from hydroxylamine derivatives (compound **73** for example) was fully described by Vasella *et al.* [41, 42] and allowed the synthesis of several interesting biologically active molecules. Similar reactions with more hindered sugar derived ketonitrones like compound **74** were first described by Tronchet et Mihaly but the yields were not reported (Scheme 18) [43].



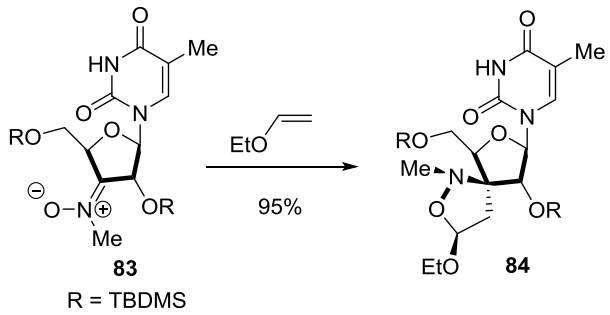
Scheme 18. 1,3-Dipolar cycloaddition reactions of carbohydrate derived aldonitrones and ketonitrones

Later, nitrone **76** was prepared from the corresponding 4-oxo-mannopyranose derivative and the cycloaddition reaction with ethyl vinyl ether afforded in a regioselective manner cycloadducts **77** and **78** with a 6:1 ratio (Scheme 19) [44]. An intramolecular version of this reaction was next investigated on various pyrano or furano derivatives bearing a 4-*O*-allyl group as the internal dipolarophile. For example, on compound **79** (α C4-hydroxyl); the reaction proceeded with good yield and in this case a single stereoisomer **80** was isolated. Starting from **81** isomer (β C4-hydroxyl), the exclusive formation of the adduct **82** was observed. These results clearly showed that the stereochemistry of the reaction depends on the C4 configuration. Others heterocyclic and carbocyclic systems were efficiently obtained by this method from carbohydrates derivatives.



Scheme 19. Examples of heterocyclic and carbocyclic systems obtained by 1,3-dipolar cycloaddition reactions

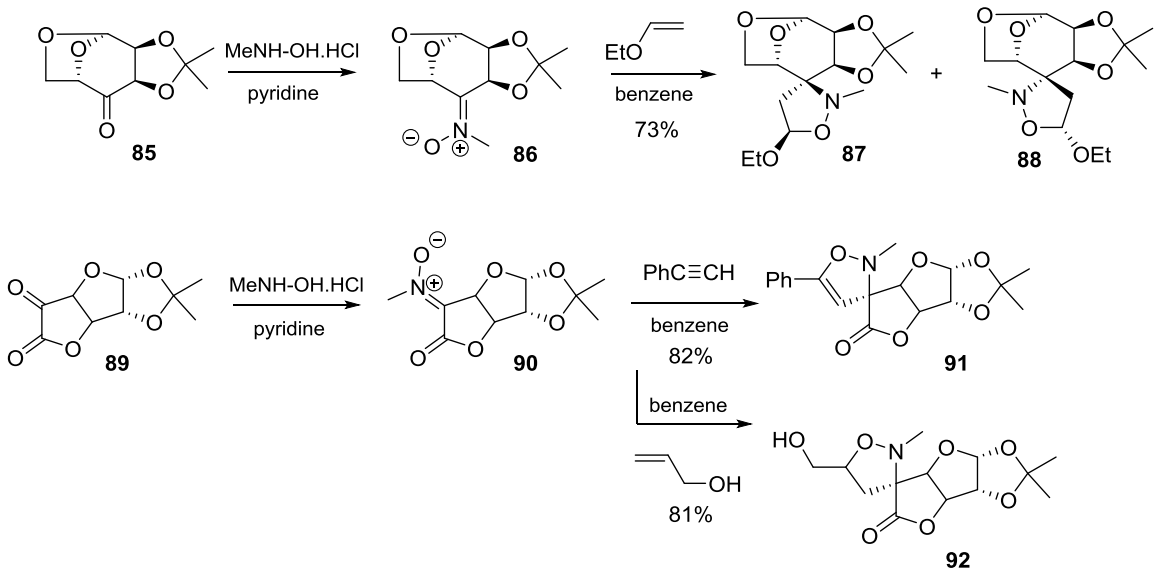
Nucleosides analogues with C2' or C3' spiro substitutions were prepared *via* intramolecular cycloaddition reactions between an electron-rich olefin and a vicinal nitrone (Scheme 20) [45, 46]. As an example, for synthesis of 3'-substituted spiro-isoxazolidine thymidine derivative **84**, the reaction of 3'-ketone with *N*-methylhydroxylamine hydrochloride gave the 3'-methylnitrone **83** susbsequently treated with ethyl vinyl ether. The cycloaddition reaction occurred in a diastereospecific manner, giving only compound **84** in 95% yield. The stereochemistry of the cycloadduct was explained by a postulated transition state and the C3'- (or C2'-) configuration was proved by 1D NOE difference spectroscopy. Other 2' or 3'- spiro-isoxazolidines derivatives were efficiently prepared by this methodology and consitute a new class of nucleoside analogues.



Scheme 20. Examples of spiro-isoxazolidine derivatives of thymidine obtained by 1,3-dipolar cycloaddition reactions

The 1,3-dipolar cycloaddition of sugar ketonitrones with differently substituted dipolarophiles was studied by Alonso *et al*. [47]. The aim of this work was to take advantage of this useful synthetic procedure to get original compounds with nitrogenated quaternary centers. The authors firstly developed highly efficient intramolecular procedures with mono-, di- and trisubstituted olefins. They then turned to an intermolecular version with ketonitrone **85**

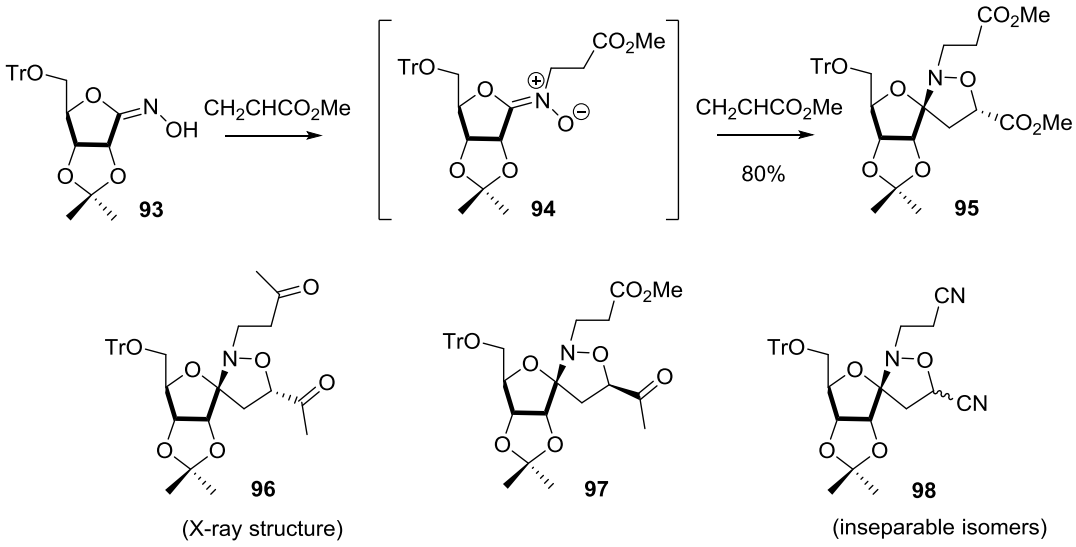
prepared by treatment of the corresponding lactone with methylhydroxylamine hydrochloride in pyridine (Scheme 21). When heated in refluxing benzene with ethyl vinyl ether, nitrone **86** led to cycloadducts **87** and **88** in 73% overall yield. The reaction occurred in a complete regioselective manner, but with a moderate stereoselectivity as attested by the **87**/**88** ratio (6:1). To go further, the authors studied the reactivity of ketonitrone **90**, directly available from D-glucurono-3,6-lactone. This tricyclic compound is an attractive system due to its high facial selectivity and can thus led to only one stereoisomer. When refluxed in benzene with phenylacetylene, expected spiro-isoxazolidine **91** was obtained in a total regio- and stereoselective manner. A complete regio and stereocontrol was also observed with allyl alcohol, leading to cycloadduct **92** in excellent yield. Only one stereoisomer was obtained but the configuration of the newly created asymetric carbon bearing the hydroxymethyl group was not established. It is worthy to note that the use of substituted dipolarophiles like 2-methyl-2-propen-1-ol gave low diastereoselectivity.



Scheme 21. 1,3-dipolar cycloaddition of sugar ketonitrones

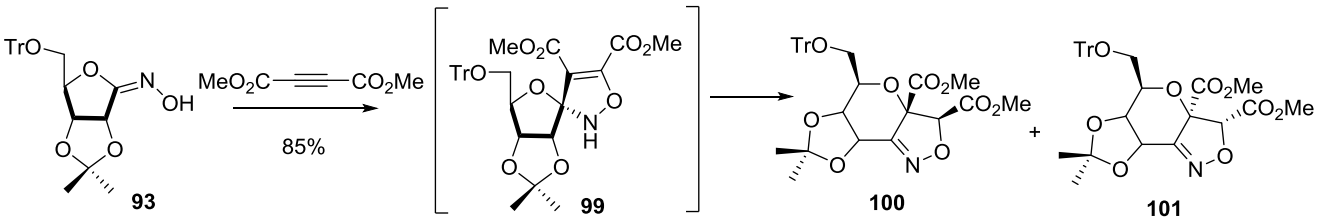
3.2. Anomeric sugar based nitrones

Chiral isoxazolidines bearing a sugar moiety have been extensively developped by Yokoyama *et al. via* a tanden Michael addition-1,3-dipolar cycloaddition [12, 48, 49]. These authors described the preparation of sugar nitrone **94** by reaction of sugar oxime **93** with methyl acrylate. The intermediate nitrone **94**, prepared according to Griggs's reaction [50], was not isolated and reacted with another methyl acrylate molecule in a 1,3-dipolar cycloaddition reaction (Scheme 22). For this purpose, the mixture was heated in dry toluene in a sealed tube and gave the spiro-isoxazolidine **95** in a regio- and stereoselective manner. The cycloadducts **96** and **97** were obtained in 48% and 37% yield respectively by reaction with methyl vinylketone. The stereochemistry of compound **96** at C3 position was umambigusly determined by X-ray analysis. When reacted with acrylonitrile, an inseparable mixture of C-3 stereoisomers **98** was obtained.



Scheme 22. Sugar hydroximolactones in a tandem Michael addition-1,3-dipolar cycloaddition

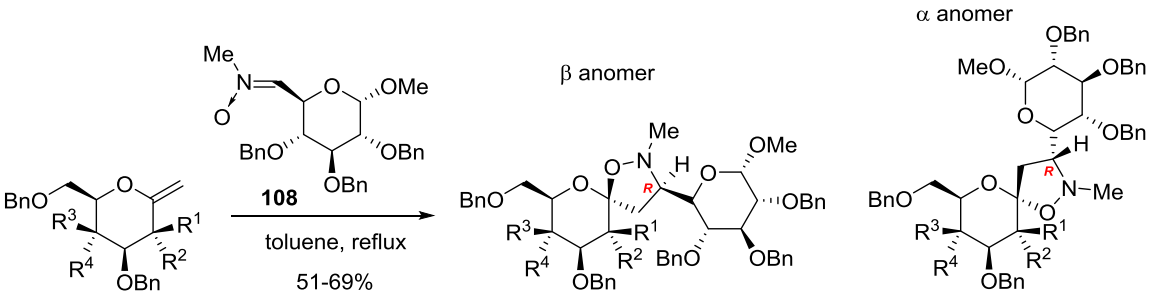
Yokoyama *et al.* also reported the preparation of two new bicyclic nucleosides **100** and **101** [51]. The formation of these original fused sytems is presumed to proceed through a spiro-isoxazoline intermediate **99** prepared by cycloaddition of dimethyl acetylenedicarboxylate and sugar oxime **93**. Instability of spiro adduct **99** prompts the opening and consecutive closure of the sugar ring and **100** and **101** were obtained in a 2.7:1 ratio as diastereoisomeric mixture in 85% overall yield (Scheme 23).



Scheme 23. New bicyclic nucleosides from hydroxyiminolactone

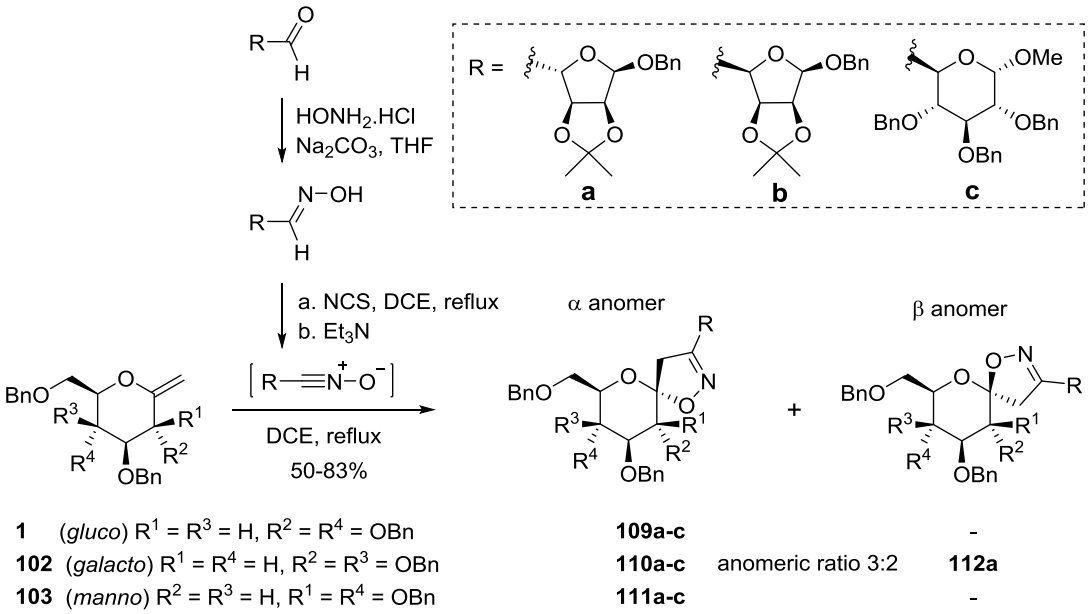
3.3. Reactions of carbohydrate derived nitrones and nitrile oxides on *exo*-methylene sugars

In connection to their work on *exo*-methylene sugars (cf I.1), Ikegami and coworkers carried out the diastereoselective cycloaddition of sugar nitrone **108** on *exo*-glycals **1**, **102** and **103** (Scheme 24) [39]. On glucose derivative **1**, reaction afforded α and β spiro-isoxazolidines **104** and **107** with a 3:1 ratio in a 69% overall yield. NOE correlations analysis enabled assignment of absolute configuration of C-6 as *R* for both anomers. In the case of galacto- and manno-*exo*-glycals **102** and **103**, only β anomers **105** and **106** were obtained in average yields.



Scheme 24. Reaction between *exo*-glycals and sugar nitrone

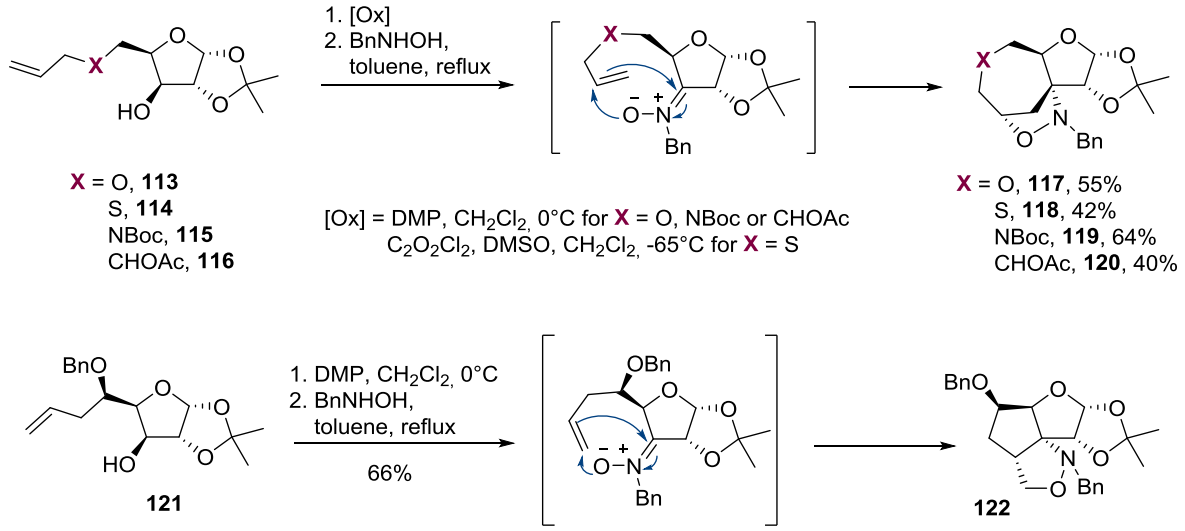
Similarly, cycloadditions between pyrano-*exo*-glycals **1**, **102** and **103** and nitrile oxides were reported by Zhang et al. (Scheme 25) [52]. Preparation of sugar nitrile oxides **a-c** involved formation of oximes from aldehydes followed by oximes chlorination and finally dehydrochlorination of oximinoyl halides. Handling of nitrile oxides **a-c** proved complex and they were used in the next step without work-up or purification. When cycloaddition reaction was carried out on glucose and mannose derivatives **1** and **103**, only α anomers **109a-c** and **111a-c** were obtained in all cases, indicating a diastereoselective addition. Concerning olefin **102**, reaction was stereoselective with nitrile oxides **b** and **c** but a 3:2 anomeric mixture was obtained with nitrile oxide **a**. It should be noted that a nitrile oxide dimer side product was also formed in all cases, probably due to instability of nitrile oxides **a-c**. After deprotection of the saccharidic spiro-isoxazolines by catalytic hydrogenation, their biological properties as glycosidases inhibitors were tested. Although the compounds showed a low inhibitory effect, they were selective between glycosidases, with a higher inhibitory activity against α-amylase.



Scheme 25. Reaction between *exo*-glycals and sugar nitrile oxides

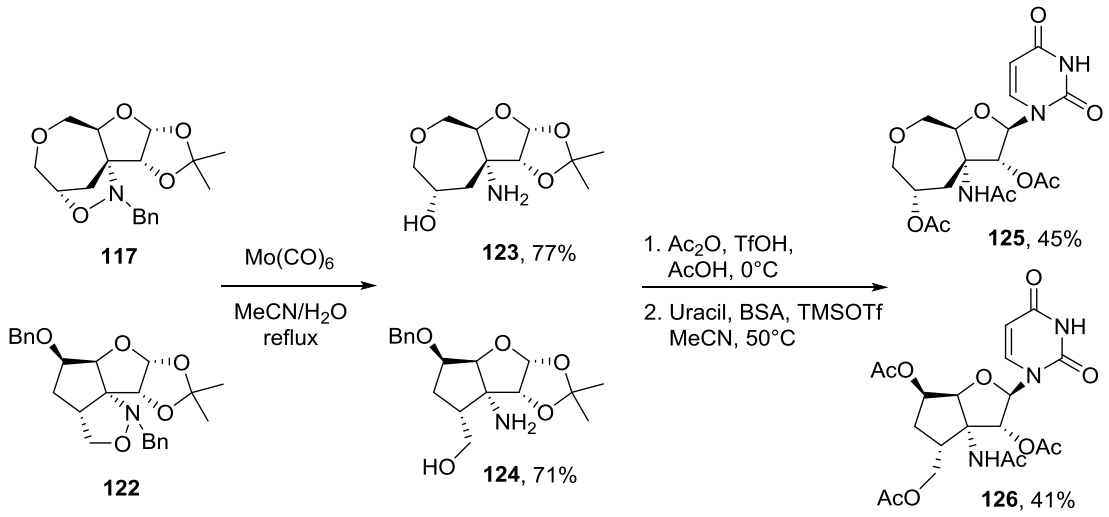
3.4. Intramolecular cycloadditions

Recently, Das *et al.* published some examples of intramolecular cycloadditions on unsaturated sugar nitrones (Scheme 26) [13]. Starting from sugar olefins **113-116**, the alcohol function was oxidized by Dess-Martin Periodinane (DMP) or oxalyle chloride and dimethylsulfoxide, followed by condensation of *N*-benzyl hydroxylamine on the aldehyde. The unstable nitro compounds underwent intramolecular cyclization to furnish exclusively seven-membered rings spiro-isoxazolidines **117-120**. Stereochemistry of the cycloadducts was assigned with NMR analysis and X-Ray crystallography. This method thus enables the formation of furanose-fused oxepane (**117**), thiepane (**118**), azepane (**119**) and cycloheptane (**120**). In the case of olefin **121**, attack of the oxanion occurred on the unsubstituted carbon of the double bond, leading to five-membered carbocycle **122** in good yield.



Scheme 26. Intramolecular nitro-olefin cycloaddition

Furthermore, they took advantage of the labile nature of the N-O bond to prepare original bicyclic nucleosides derivatives (Scheme 27). Cleavage of the isoxazolidine ring of **117** and **122** was carried out with molybdenum hexacarbonyl in refluxing aqueous acetonitrile, leading to **123** and **124** in 77 and 71% yields respectively. After deprotection of the sugar 1,2 diol of compounds **123** and **124** and subsequent acetylation of the free amino and hydroxyl groups, the fully protected compounds underwent glycosylation in Vorbrüggen conditions to give nucleosides **125** and **126** in 45 and 41% yields.



Scheme 27. Preparation of bicyclic nucleosides

4. Conclusion

The 1,3-dipolar cycloaddition reaction between an olefin and a nitrile oxide or a nitrone is an efficient way to prepare isoxazolines and isoxazolidines, respectively. The adaptation of this reaction on saccharidic systems has been studied in the literature for several decades. In this chapter, we put the emphasis on the preparation of saccharidic spiro derivatives containing these heterocycles, an unexplored subject until the preliminary results of Rajanbabu *et al*. in 1986. Since then, the syntheses of saccharidic spiro-isoxazoli(di)nes have been expanded on various types of olefins, notably *exo*-methylene sugars or activated *exo*-glycals. The cycloaddition proceeds in many cases with high regio- and stereocontrol and the stereochemistry of adducts can be established by NMR experiments and/or X-ray analyses. Elegant examples involving sugar-based nitrile oxides and nitrones and also intramolecular cycloadditions were reported and paved the way to the preparation of original bicyclic systems and various carbocycles. In several examples, the properties of the obtained saccharidic cycloadducts were investigated for various biological applications such as spironucleoside analogues, antibacterial agents or enzyme inhibitors. In addition to their biological properties and taking into account the originality of their structures, these systems were utilized as sugar scaffolds and proved suitable for selective derivatization.

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