New chemical transformations of sugar imine and glycal derivatives

Closing report

Project N^{o} FK_128766 (2018-2022)

The main goal of this research proposal was to develop new synthetic methodologies to extend the toolkit of synthetic carbohydrate chemistry ensuring easier availability of new multifunctional building blocks by

1) metal-catalyzed and metal-free coupling reactions of anhydro-aldose and aldono-lactone tosylhydrazones,

2) various chemical transformations of 1-*C*-substituted-glycal and *exo*-glycal derivatives.

This report is constructed to follow that aims which were formulated in the research plan. The results which have already been published are described in a concise manner with references to the publications, while others which await for publication are presented in details.

Aim 1. Study of the coupling reactions of anhydro-aldose and aldono-lactone tosylhydrazones

To study the cross-coupling reactions of anhydro-aldose tosylhydrazones (*C*-(glycopyranosyl)formaldehyde tosylhydrazones) such type of starting materials, *O*-peracetylated *C*-(β-D-galactopyranosyl)formaldehyde and *C*-(α-D-mannopyranosyl)formaldehyde tosylhydrazones, *O*-perbenzoylated *C*-(β-D-glucopyranosyl)formaldehyde and (α-D-mannopyranosyl)formaldehyde tosylhydrazones were synthesized in a four-step reaction from the corresponding free sugars. To get anhydro-aldose tosylhydrazones with base-stable protecting groups, synthetic methods were elaborated for the synthesis of *O*-permethylated *C*-(β-D-glucopyranosyl)formaldehyde and *C*-(β-D-mannopyranosyl)formaldehyde and *O*-permethoxymethylated *C*-(β-D-galactopyranosyl)formaldehyde tosylhydrazones. Synthesis of *O*-perbenzylated gluco derivative failed due to the unsuccessful synthesis of *O*-perbenzylated β-D-glucopyranosyl-formaldehyde.
Publication: ***Pure Appl. Chem.*** **2019*, 91* (7), 1159-1175.** https://doi.org/10.1515/pac-2019-0208

To find a readily available and less toxic cyano source instead of $Hg(CN)_2$, the key reagent of the glycopyranosyl cyanide (starting material of *C*-(glycopyranosyl)formaldehyde tosylhydrazones) synthesis, *O*-peracylated glycosyl-bromides and -iodides were synthesized and reacted with zinc(II) cyanide, copper(I) cyanide, silver (I) cyanide and tetrabutylammonium cyanide in different dipolar aprotic solvents. Structural elucidation of the obtained products by NMR revealed the formation of 1,2,3,4,6-penta-*O*-acetyl-D-glycose and 2,3,4,6-tetra-*O*-acetyl glycose instead of the desired cyano product.

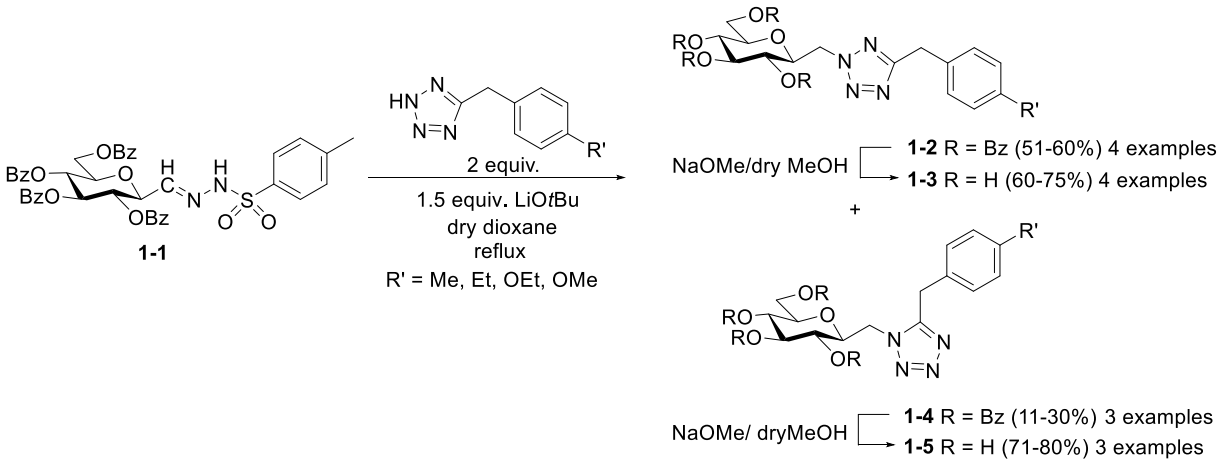
C-N bond formation reactions of anhydro-aldose tosylhydrazones

Coupling reactions of *O*-peracylated 2,6-anhydro-aldose tosylhydrazones (*C*-(β-D-glycopyranosyl)formaldehyde tosylhydrazones) with tetrazoles were studied under metal-free

conditions using thermic or microwave activation in the presence of different bases. The reactions proved highly regioselective and gave the corresponding, up-to-now unknown 2-β-D-glycopyranosylmethyl-2*H*-tetrazoles in 7-67% yields. The method can be applied to get new types of disaccharide mimetics, 5-glycosyl-2-glycopyranosylmethyl-2*H*-tetrazoles, as well. Galectin binding studies with *C*-(β-D-galactopyranosyl)formaldehyde tosylhydrazone and 2-(β-D-galactopyranosylmethyl)-5-phenyl-2*H*-tetrazole revealed no significant inhibition of any of these lectins.
Publication: ***Org. Biomol. Chem.*** **2021,** ***19,*** **605-618.** https://doi.org/10.1039/D0OB02248A

To extend the above catalyst-free couplings to aromatic derivatives, aromatic *N*-tosylhydrazones were synthesized and coupled with tetrazoles using thermic activation in the presence of different bases. The reactions proved to be highly regioselective to result in the corresponding 2,5-disubstituted-2*H*-tetrazoles as main products and 1,5-disubstituted-1*H*-tetrazoles as minor products. Owing to its mild conditions, the method enabled the use of a wide range of substrates.
Publication: ***Eur. J. Org. Chem.*** **2022.** https://doi.org/10.1002/ejoc.202201103

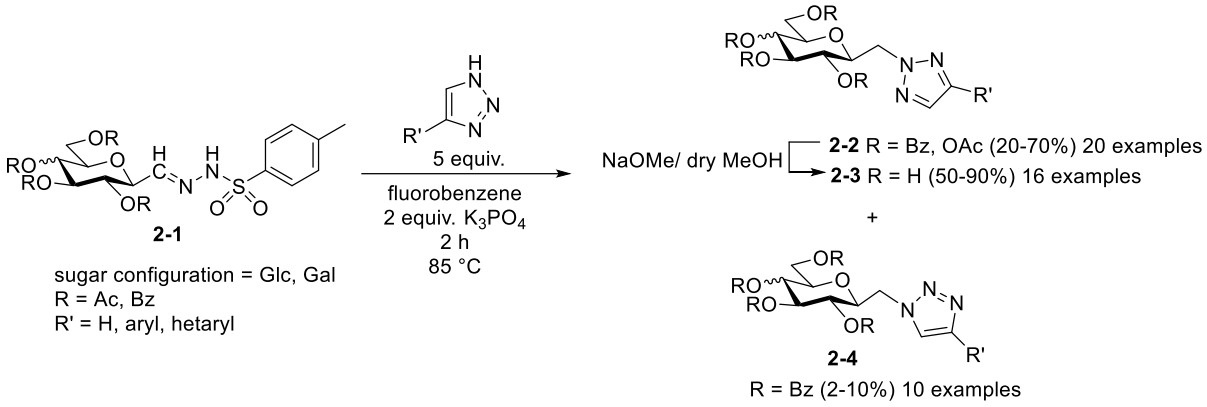
5-Substituted (p-Me, p-Et, p-OMe, p-OEt) benzyl-2*H*-tetrazoles were synthesized from the corresponding aldehydes in a two-step reaction and coupled with *O*-perbenzoylated *C*-(β-D-glucopyranosyl)formaldehyde tosylhydrazone **1-1** to form new SGLT2 (renal sodium dependent glucose co-transporter 2) inhibitors as antidiabetics. These types of tetrazoles were predicted to be stronger inhibitors than dapagliflozin (the first active molecule against SGLT2). Deprotection of the coupled products **1-2** and **1-4** were carried out by the Zemplén method to form **1-3** and **1-5** derivatives (Scheme 1). The biological measurements are in progress in the Department of Medical Chemistry of the University of Debrecen by Dr. Tibor Docsa. ***These results will be published after the biological studies.***



Scheme 1: Coupling of *O*-perbenzoylated *C*-(β-D-glucopyranosyl)formaldehyde tosylhydrazone with 5-substituted benzyl-2*H*-tetrazoles to form potential SGLT inhibitors

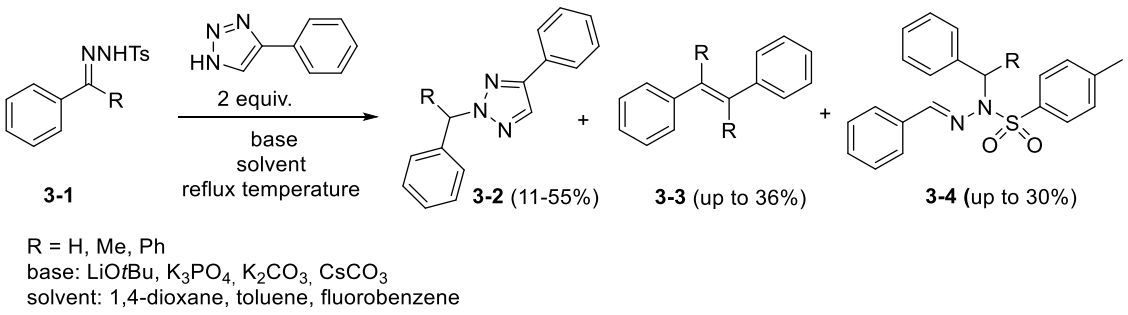
1-β-D-Galactopyranosylmethyl 4-aryl-1,2,3-triazoles were reported as selective galectin-1 inhibitors. To get a more detailed SAR, synthesis of the regioisomer 2-β-D-galactopyranosylmethyl 4-aryl-1,2,3-triazoles were carried out with the extension of the catalyst free C-N coupling reactions of anhydro-aldose tosylhydrazones for 4-aryl/hetaryl-1*H*-1,2,3-triazoles, which were synthesized from the corresponding benzaldehydes in a two-step reaction *via* β-nitrostyrenes. Gluco derivatives were also synthesized as potential GP (glycogen

phosphorylase) inhibitors. Optimization reactions were carried out with *O*-perbenzoylated *C*-(β-D-glucopyranosyl)formaldehyde tosylhydrazone (**2-1**, Glc, R = Bz) and 1*H*-1,2,3-triazole to find K_3PO_4 – fluorobenzene – thermic activation as optimized reaction conditions (isolated yield: 70%). Coupling reactions of *O*-perbenzoylated *C*-(β-D-glucopyranosyl)formaldehyde tosylhydrazone (**2-1**, Glc, R = Bz) with 4-aryl-1*H*-1,2,3-triazoles resulted regioselectively in 2,4- (35-63%) (**2-2**, Glc, R = Bz) and 1,4-disubstituted (2-10%) (**2-4**, Glc, R = Bz) 1,2,3-triazoles. On the other hand, with *O*-peracetylated *C*-(β-D-galactopyranosyl)formaldehyde tosylhydrazone (**2-1**, Gal, R = Ac) exclusively 2,4-disubstituted 1,2,3-triazoles (**2-2**, Gal, R = Ac) were formed in lower yields (20-38%) (Scheme 2). Galectin inhibition studies of the unprotected 4-aryl-2-galactopyranosylmethyl-1,2,3-triazoles (**2-3**, Gal, R = H) are in progress in the Lund University by Ulf Nilsson's group. The gluco derivatives (**2-3**, Glc, R = H) are examined against GP in the Department of Medical Chemistry of the University of Debrecen by Dr. Tibor Docsa. ***These results will be published after the biological studies.***



Scheme 2: Coupling of *C*-(β-D glycopyranosyl)formaldehyde tosylhydrazones with 1*H*-1,2,3-triazole and 4-aryl/hetaryl-1*H*-1,2,3-triazoles

Although 1,2,3-triazoles have versatile biological (antimicrobial, antihypertensive and anti-AIDS) activities, comparatively fewer methods are available for the preparation of 2,4-diaryl-1,2,3-triazoles. Thus, the above-mentioned catalyst-free coupling was extended to aromatic *N*-tosylhydrazones **3-1**. The first optimization reactions with benzaldehyde tosylhydrazone **3-1** (R = H) and 4-phenyl-1*H*-1,2,3-triazole resulted regioselctively in 2,4-disubstituted 1,2,3-triazoles **3-2** with moderate yields (Scheme 3). Stilbene derivatives **3-3**, formed in a carbene dimerization reaction, and *N*-substituted tosylhydrazones **3-4**, formed in a carbene insertion into the N-H bond of tosylhydrazone **3-1**, were also isolated from the reaction mixtures. Further optimization is in progress.



Scheme 3: Optimization on coupling reactions of *N*-tosyhydrazones with 4-phenyl-1*H*-1,2,3-triazole

C-N coupling reactions of *C*-(β-D-glycopyranosyl)formaldehyde tosylhydrazones with primary and secondary amines (morpholine and piperidine), with aniline derivatives (4-anisidine, 2-naphthylamine, 2-aminopyrimidine), with pimary amides (cyanamide, benzenesulfonamide) and with *N*-heterocycles (other than tetrazoles and 1,2,3-triazoles: barbituric acid, 2-hydroxybenzimidazole, imidazole, indole, indole-3-carboxaldehyde, isatin, 5-phenylhydantoin, phthalimide) were also studied, but resulted in multicomponent product mixtures under transition-metal catalysed ($Cu(acac)_2$ or $Pd(PPh_3)_2Cl_2$) or metal-free conditions, as well. Their separation did not allow the isolation of the coupled products in pure form.

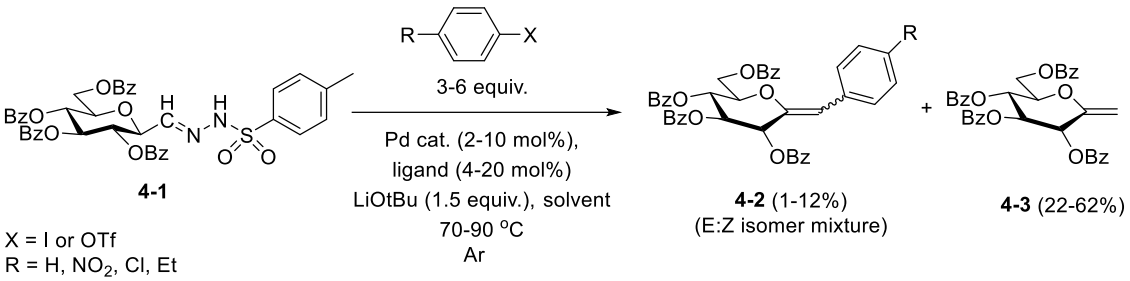
C-C bond formation reactions of anhydro-aldose tosylhydrazones

A catalyst-free coupling reaction between *O*-peracetylated, *O*-perbenzoylated, *O*-permethylated, and *O*-permethoxymethylated 2,6-anhydro-aldose tosylhydrazones (*C*-(β-D-glycopyranosyl)formaldehyde tosylhydrazones) and aromatic boronic acids were also reported. The base-promoted reaction is operationally simple and exhibits a broad substrate scope. The main products in most of the transformations were the open-chain 1-*C*-aryl-hept-1-enitol type compounds while the expected β-D-glycopyranosylmethyl arenes (benzyl *C*-glycosides) were formed in subordinate yields only. A mechanistic rationale is provided to explain how a complex substrate may change the well established course of the reaction.
Publication: ***Molecules*** **2022,** ***27*** **(6), 1795.** https://doi.org/10.3390/molecules27061795

Pd-catalyzed cross-coupling reactions of *O*-peracetylated (β-D-galactopyranosyl)formaldehyde and *O*-perbenzoylated (β-D-glucopyranosyl)formaldehyde tosylhydrazones or its Li-salts with arylboronic acids were also studied, but the desired substituted *exo*-glycals were isolated only in traces.

In the field of coupling of anhydro-aldose tosylhydrazones with terminal alkynes, lithium- and sodium phenylacetylides were reacted with *O*-peracetylated *C*-(β-D-galactopyranosyl)- and *C*-(2,3,4,6-tetra-*O*-methyl-β-D-glucopyranosyl)formaldehyde tosylhydrazones in catalyst free or in Pd- or Cu-catalyzed reactions. These transformations resulted in complex reaction mixtures from which *exo*-galactal (formed in an intramolecular C-H insertion reaction) and galactal-aldehyde (formed *via* successive hydrolytic and elimination step) were isolated. These reactions were extended to other CH-acidic compounds (barbituric acid and Meldrum's acid), but formation of the coupled products was not observed.

To extend our previously reported Pd-catalyzed coupling reactions of anhydro-aldose tosylhydrazones with aryl bromides, *O*-perbenzoylated *C*-(β-D-glucopyranosyl)formaldehyde tosylhydrazone **4-1** was reacted with aryl-triflates and *p*-nitroiodobenzene, in the presence of various Pd catalysts, ligands and bases. The main product of these couplings was *exo*-glucal **4-3** instead of the desired coupled product **4-2** (Scheme 4).



X = I or OTf
R = H, NO_2, Cl, Et
Pd cat.: $PdCl_2$, $Pd(OAc)_2$, $Pd_2(dba)_3$
ligand: CataCXium A, tri(2-furyl)phosphine, 1,1'-bis(diphenylphosphino)ferrocene, 1,3-bis(diphenylphosphino)propane, XPhos, Ph_3P
solvent: 1,4-dioxane, fluorobenzene, toluene

Scheme 4: Coupling *of O*-perbenzoylated *C*-(β-D-glucopyranosyl)formaldehyde tosylhydrazone with 4-iodonitrobenzene and phenyl triflates

C-C and C-N bond formation reactions of aldono-lactone tosylhydrazones

For studying of coupling reactions of aldono-lactone tosylhydrazones, *O*-perbenzylated and *O*-peracetylated D-glucono-1,5-lactone tosylhydrazones were prepared in gram scales in multistep reactions.

Couplings of aldono-lactone tosylhydrazones and their Na-salts with phenyl-boronic acid were studied in catalyst-free and Pd- and Cu-catalyzed reactions under thermic and photolytic conditions. However, these couplings did not lead to the desired coupled products.

Pd-catalyzed coupling reactions of aldono-lactone tosylhydrazones and their Na-salts with bromobenzene and benzyl bromide derivatives were investigated. These reactions resulted in an elimination product instead of the coupled derivatives.

Next, the formation of the C-N bond using *O*-perbenzylated D-glucono-1,5-lactone tosylhydrazone or its Na-salt as substrates was investigated. Coupling of phenyltetrazole in the presence of various bases and solvents under thermic or photolytic conditions did not give the expected coupled product. Only pyrrolidine, morpholine and piperidine gave desired C-N coupled products in low to moderate yields.

Aim 2. Study of the chemical transformations of 1-C-substituted glycal and exo-glycal derivatives

Transformations of *exo*-glycals

Study of [2+2] cycloaddition reactions of exo-glycals

We studied up-till-now unexplored [2+2] cycloaddition reactions of several *exo*-glycals with chlorosulfonyl isocyanate (CSI) and dichloroketene. The addition of CSI took place with excellent regioselectivity with a strong dependence on the protecting groups of *exo*-glycals and the reaction temperature. While acetylated *exo*-glucal, -galactal, -mannal and -xylal gave the 1'*S* and 1'*R* isomers of spiro β-lactams with a 1'*S* preference (32%-11% vs. 3%-16%), the 1'*S* isomer was formed exclusively (42%) from the benzoylated *exo*-glucal. The stability of the β-

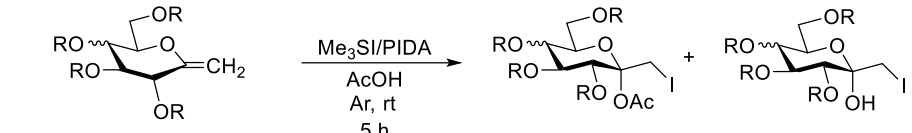
lactam ring depended on the temperature, and at higher temperature acyclic, ring-opened side-products were formed.
The addition of dichloroketene to *exo*-glycals took place with excellent regioselectivity, but the *in situ* didehalogenation of the cycloadducts failed in the case of acetylated *exo*-galactal, *exo*-*xylal* and benzoylated *exo*-glucal. The diastereomeric mixtures of the monohalogenated spiro-cyclobutanones that were formed, could be dehalogenated in a further step (45%-65%). Contrary to this, the didehalogenation of the cycloadduct of benzoylated 2-deoxy-*exo*-glucal and acetylated *exo*-mannal took place in one step and the desired spirocyclobutanone was isolated in moderate or good yield (25%-45%). The Baeyer-Villiger oxidation of a spirocyclobutanone gave a 1 : 1 mixture of spiro epimeric γ-lactones.
A manuscript of this research results has been submitted for publication to Eur. J. Org. Chem., Manuscript number: ejoc.202201488

Thiol-ene additions of some new exo-glycal derivatives

O-Peracylated and -perbenzoylated *exo*-mannal, *exo*-glucal and *exo*-galactal derivatives were synthesized from the corresponding anhydro-aldose tosylhydrazones and photoinitiated thiol-ene additions of these compounds were studied in a collaboration to result in the corresponding *C*-(mannopyranosyl/mannofuranosyl/glucopyranosyl/galactopyranosyl)methyl sulfides in medium to good yields with exclusive regio- and β-(D) stereoselectivities.
Publications: ***RSC Adv.*** **2020,** ***10,*** **34825-34836** https://doi.org/10.1039/D0RA07115C **and** ***Int. J. Mol. Sci.*** **2020,** ***21,*** **573** https://doi.org/10.3390/ijms21020573

Other functionalization of exo-glycals

Acetoxyiodination of *exo*-glycals **5-1** and **5-3** were studied with Me_3SI/PIDA/AcOH/Ar/r.t. While the reaction of *O*-perbenzoylated *exo*-glucal resulted in the desired acetoxyiodinated derivative **5-2** as a single product in moderate yield, in the case of *O*-peracetylated *exo*-galactal two products (acetoxyiodinated **5-4** and hydroxyiodonated compounds **5-5**) were isolated with moderate yields (Scheme 5).



5-1 Sugar configuration: Glc; R = Bz
5-3 Sugar configuration: Gal; R = Ac

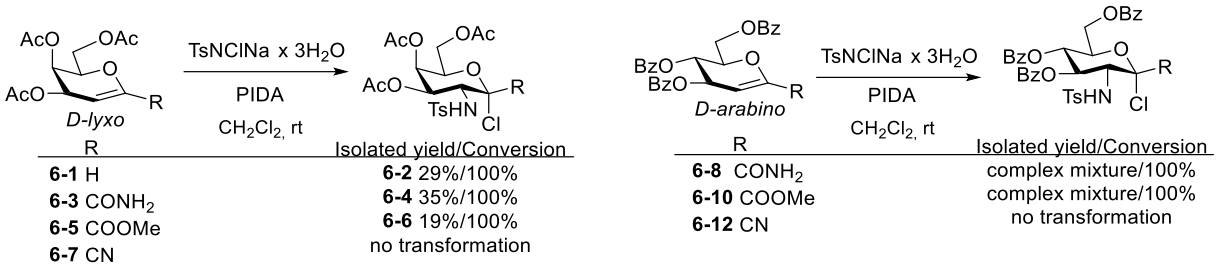
5-2 (22%)
5-4 (37%)

5-5 (22%)

Scheme 5: Acetoxiiodination of *O*-peracylated *exo*-glycals

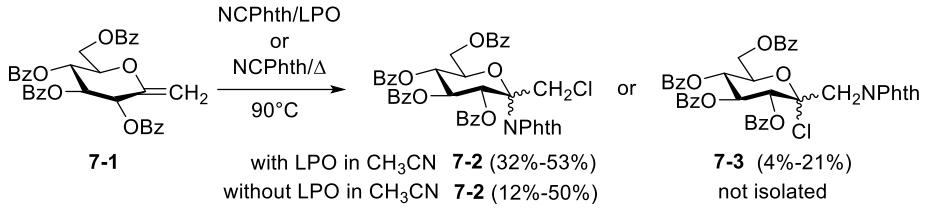
Study of haloamidation reactions of exo-glycals and 1-C-acceptor-substituted glycals

Chloroamidation of *O*-peracetylated galactal **6-1**, and D-*lyxo* and D-*arabino* configured 1-C-acceptor-substituted glycals **6-3**, **6-5**, **6-7** **6-8**, **6-10** and **6-12** were studied in the presence of chloramine-T/PIDA reagents. The desired haloamidated products **6-2**, **6-4** and **6-6** from compounds **6-1**, **6-3** and **6-5** were isolated in moderate yields (19%-35%). Transformations of D-*arabino* configured 1-*C*-substituted glycals **6-8** and **6-10** were unsuccessful to give an inseparable, complex mixture. The nitrile substituted derivatives **6-7** and **6-12** did not react under these conditions (Scheme 6).



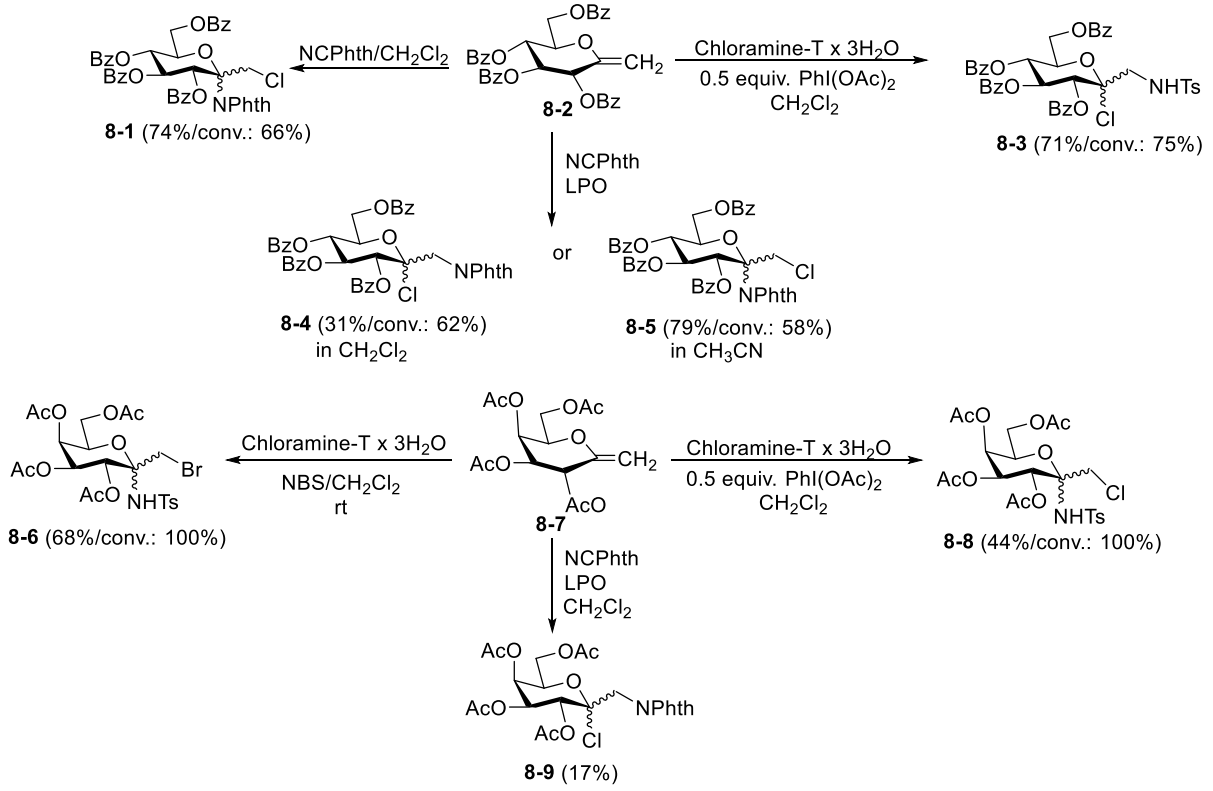
Scheme 6: Haloamidation of 1-C-acceptor-substituted glycals

Optimization reactions and mechanistic studies of chloroamidation of *O*-perbenzoylated *exo*-glucal **7-1** with *N*-chlorophthalimide in the presence of LPO (radical precursor) and without LPO in thermal conditions were performed. The desired regioisomers **7-2** and **7-3** were synthesized in moderate to good yields with high or complete regioselectivity (Scheme 7).



Scheme 7: Haloamidation of *O*-perbenzoylated *exo*-glucal **7-1**

Chloroamidation of *O*-perbenzoylated *exo*-glucal **8-2** and *O*-peracetylated *exo*-galactal **8-7** in the presence of *N*-chlorophthalimide or chloramin-T/PIDA reagents were carried out (Scheme 8).

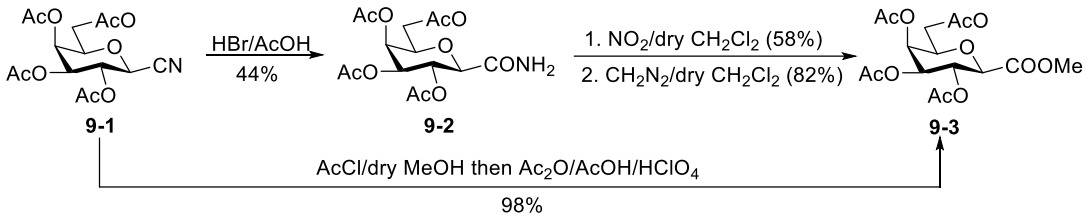


Scheme 8: Haloamidation of *exo*-glycals **8-2** and **8-7**

In the case of D-*gluco* configured **8-2** using chloramin-T/PIDA reagents the desired haloamidated product **8-3** was isolated in good yields (44% and 71%). Similar transformations of **8-2** were performed with *N*-chlorophthalimide in CH_2Cl_2 to give the regioisomer **8-1** in good yield. This transformation was also studied in the presence of LPO (dilauroyl peroxide) in CH_2Cl_2 or CH_3CN led to the formation of regioisomers **8-4** and **8-5**. Transformation of D-*galacto* configured **8-7** with chloramin-T/PIDA gave the haloamidated product **8-8** in moderate yield, and its regioisomer **8-9** was isolated using *N*-chlorophthalimide/LPO. In the case of Chloramin-T/NBS the corresponding bromoamidated compound **8-6** was isolated in good yield (68%). ***These results have been compiled in manuscripts to be submitted soon.***

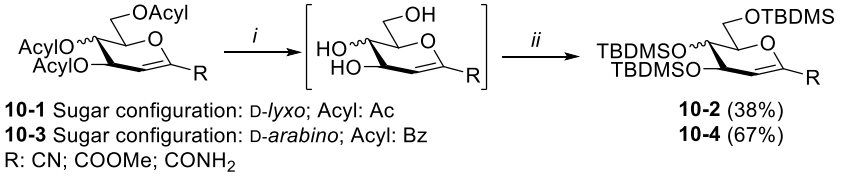
Synthesis of 1-C-acceptor-substituted exo-glycals

O-Peracetylated and *O*-perbenzoylated 1-C-substituted glycal derivatives (with CN, $CONH_2$ and COOMe substituents at the anomeric center) were synthesized from D-galactose and D-glucose in multistep syntheses (5-8 steps; 10%-18% overall yields). Because of the low overall yields, the synthetic sequence of D-*lyxo* configured glycal derivatives was optimized. First, the work up procedure of the elimination step from 1-bromo-1-carbamoyl galactose derivative was modified to increase the yield from 33% to 99%. In this optimization step the extraction of the filtered reaction mixture was skipped, and the crude product was purified by column chromatography. Secondly, the synthesis of the methoxycarbonyl derivative was simplified. Until now this compound was synthesized from nitrile derivatives in a three-step procedure (nitrile **9-1** → amide **9-2** → carboxylic acid → ester **9-3**) using harsh and toxic reagent/conditions (NO_2 generated from $Pb(NO_2)_4$ or diazomethane). This procedure was modified, and the desired compound **9-3** could be synthesized in a *one pot* type, two-step procedure (1. AcCl/dry MeOH then Ac_2O/AcOH/$HClO_4$) with quantitative yield (98% *vs.* 21%) (Scheme 9).



Scheme 9: Optimization of the synthesis of ester derivative **9-3**

TBDMS (*tert*-butyldimethylsilyl) protected 1-C-acceptor-substituted glycals were synthesized in a two-step procedure from *O*-peracylated derivatives **10-1** and **10-3**, using deprotection – protection sequences and the desired compounds **10-2** and **10-4** were isolated in moderate to good yields (38% and 67%) (Scheme 10).



10-1 Sugar configuration: D-*lyxo*; Acyl: Ac
10-3 Sugar configuration: D-*arabino*; Acyl: Bz
R: CN; COOMe; $CONH_2$

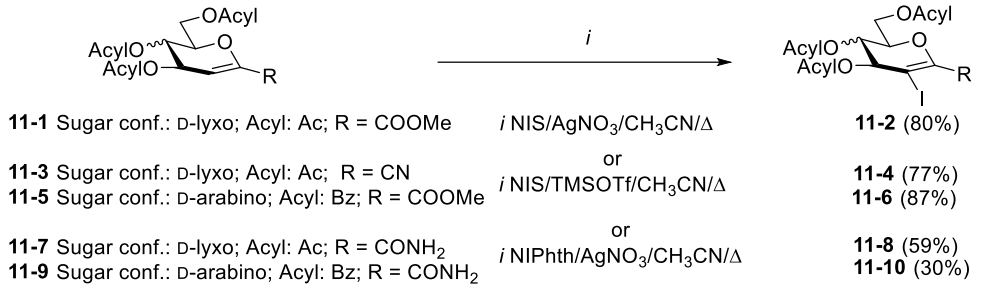
10-2 (38%)
10-4 (67%)

i NaOMe/dry MeOH or KCN/MeOH (for nitrile derivatives); *ii* TBDMSCl/imid/dry DMF

Scheme 10: Synthesis of TBDMS protected 1-C-acceptor-substituted glycals

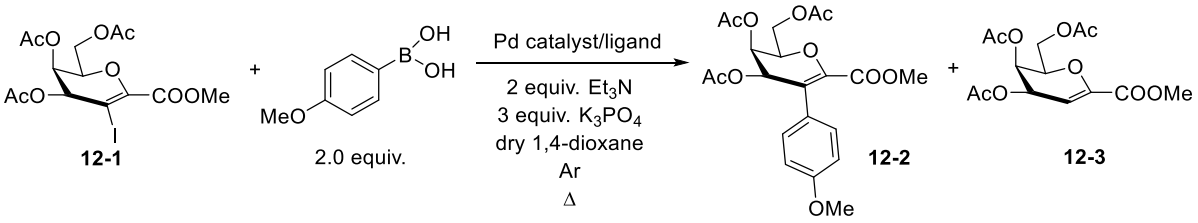
Synthesis of 2-iodo-1-C-acceptor-substituted glycals and their application in Pd-catalyzed coupling reactions

The synthesis of 2-iodo-1-C-acceptor-substituted glycals **11-2**, **11-4**, **11-6**, **11-8**, **11-10** were developed using NIS or NIPht in the presence of $AgNO_3$ or TMSOTf in CH_3CN. The corresponding iodo derivatives **11-2**, **11-4**, **11-6**, **11-8**, **11-10** were isolated in moderate to good yields (Scheme 11).



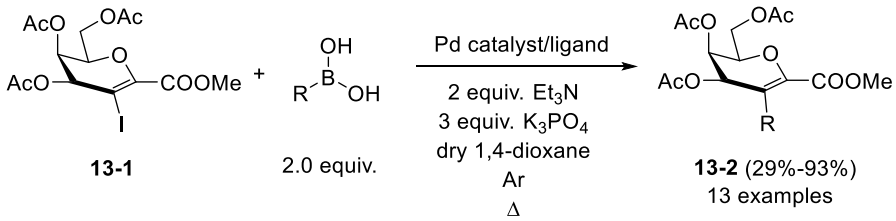
Scheme 11: Synthesis of 2-iodo-1-C-acceptor-substituted-D-*lyxo* and D-*arabino* glycals

Next Pd-catalyzed cross-coupling reactions of 2-halo compounds were investigated with different boronic acid derivatives. Optimization of reaction conditions was performed with the D-*lyxo* configured methoxycarbonyl substituted *O*-peracetylated glycal **12-1** and 4-methoxybenzene boronic acid with various Pd sources, ligands and temperature (Scheme 12). We revealed that both $Pd(OAc)_2/PPh_3$ and $Pd(PPh_3)_4$ gave the desired compound **12-2** in high yields (100% and 80%) but we also observed the formation of a dehalogenated compound **12-3** in the latter case.



Scheme 12: Optimization of Suzuki-Miyaura coupling reaction of 2-iodo-1-C-acceptor substituted glycals

With the optimized conditions in hand, we extended the series of boronic acids (applying aryl-, heteroaryl- and alkyl boronic acids) and the corresponding 1,2-di-*C*-substituted glycals **13-2** were isolated in moderate to good yields (29%-93%). We also observed, that heteroaryl and ortho substituted aryl boronic acids did not give the desired coupled products (Scheme 13).

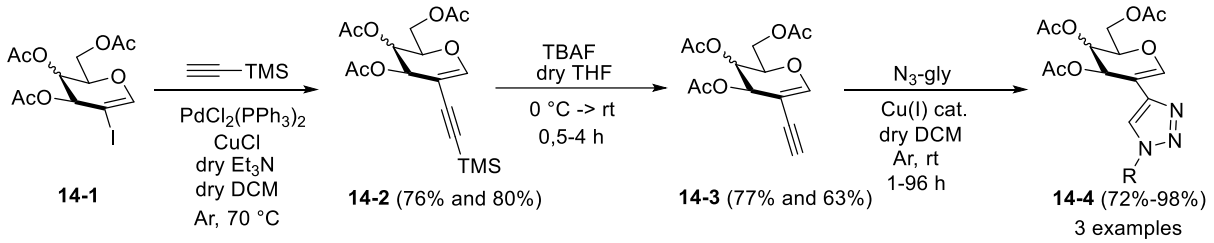


Scheme 13: Suzuki-Miyaura coupling reaction of 2-iodo-1-C-acceptor-substituted glycal

The reaction was extended to the other *O*-peracylated D-*lyxo* and *O*-perbenzoylated D-*arabino* configured 1-C-substituted glycals (CN; COOMe and $CONH_2$) and the corresponding 2-aryl derivatives were isolated in moderate to excellent yields (4 examples; 30%-89%). Surprisingly the carbamoyl substituted *O*-perbenzoylated D-*arabino* configured glycal gave an inseparable complex mixture.

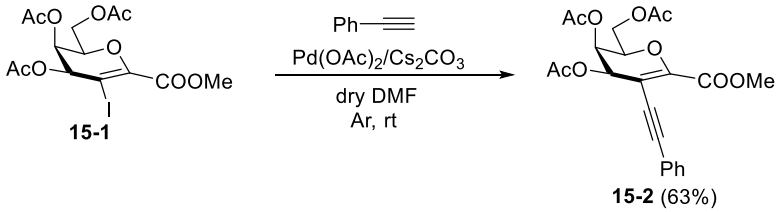
A manuscript of these research results has been submitted for publication to Adv. Synth. Catal., Manuscript number adsc.202201397

We also studied the Sonogashira coupling reaction of 2-iodo-glycals **14-1** with TMS- acetylene. *O*-peracetylated glucal and galactal **14-1** reacted with TMS-acetylene and gave TMS protected 2-ethynyl glycals **14-2**, which were deprotected with TBAF and then reacted with glycosyl-azides under the conditions of CuAAC reaction obtaining 1,4-disubstituted triazoles **14-4** in good to excellent yields (72%-98%) (Scheme 14).



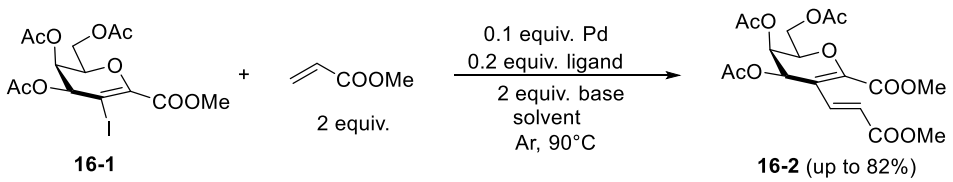
Scheme 14: Sonogashira coupling of 2-iodo-glycals and their CUAAC transformation

The reaction was extended to 2-iodo-1-C-acceptor-substituted D-*lyxo* configured *O*-peracetylated glycals (COOMe; $CONH_2$), whereby only the methoxycarbonyl substituted derivative **15-1** reacted with phenylacetylene under copper free conditions, and the desired 2-(2-phenylethynyl)-glycal **15-2** was isolated in good yield (63%) (Scheme 15). ***These results have been compiled in manuscripts to be submitted soon.***



Scheme 15: Sonogashira coupling of 2-iodo-1-C-acceptor-substituted glycals

We also optimized the Heck coupling reaction of 2-iodo-1-methoxycarbonyl-substituted *O*-peracetylated D-*lyxo* configured glycal **16-1** with methyl acrylate. We studied the effect of the base, palladium source, ligand and the solvent. We found that the optimized conditions are the following: $Pd(OAc)_2$ (0.1 equiv.)/JohnPhos (0.2 equiv.)/K_2CO_3 (2 equiv.)/dry DMF/90 °C/20 min. which resulted in the corresponding sugar-based diene **16-2** in good yield (82%) (Scheme 16). Further reactions are in progress.

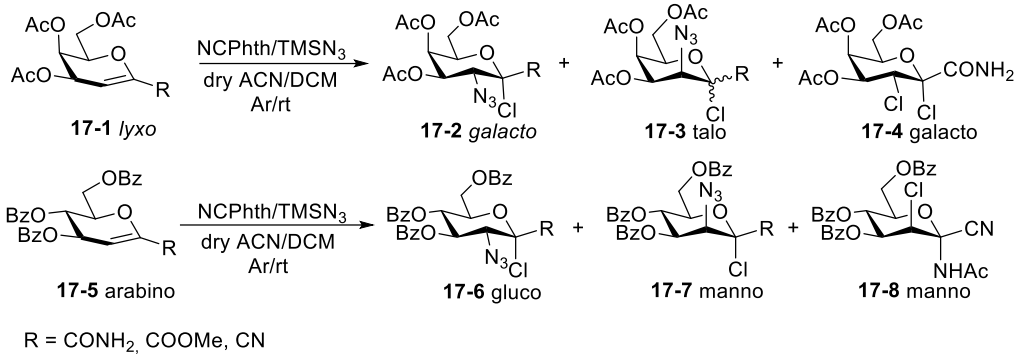


Scheme 16: Heck coupling reaction of 2-iodo-1-C-acceptor-substituted glycal

Functionalization of 1-C-aceptor-substituted glycal derivatives

Haloazidation transformation of 1-C-acceptor-substituted glycals was studied in detail under several reaction conditions (e.g.: Me_3SI/PIDA/$TMSN_3$/dry acetonitrile/0 °C – rt/Ar or NIS/$TMSN_3$/dry DCM/rt/N_2 or $Yb(OTf)_3$/NBS/$TMSN_3$/dry acetonitrile/rt/Ar; I_2/$TMSN_3$/dry DCM/rt/Ar; NCS or NCPhth/$TMSN_3$) but here only the results of the "*optimal*" conditions are summarized.

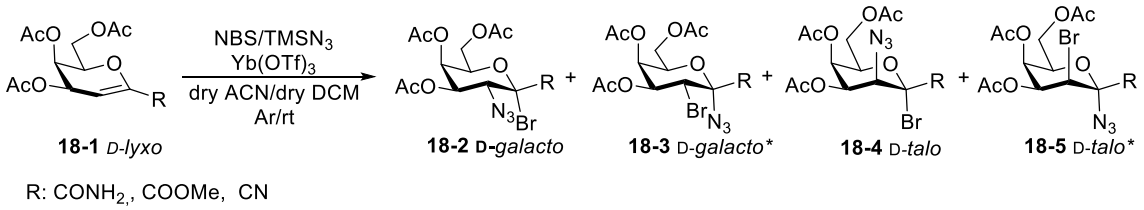
Chloroazidation reaction of these glycals **17-1** and **17-5** were carried out with *N*-chloro-phthalimide/$TMSN_3$ at r.t. under inert atmosphere (Ar). The reaction was performed in dry acetonitrile or dry dichloromethane (Scheme 17).



Scheme 17: Chloroazidation of 1-C-acceptor-substituted glycals

We observed that the reactivity of these compounds was highly dependent on the 1-C substituents and increased from CN < COOMe < $CONH_2$. In the case of D-*lyxo* configured glycals **17-1**, the carbamoyl substituted derivative (R: $CONH_2$) gave the D-*galacto* configured chloroazidated compound **17-2-CONH$_2$** in good yield (57%) beside some D-*galacto* configured dichlorinated compound **17-4-CONH$_2$** (6%) in dry dichloromethane. The methoxycarbonyl **17-1-COOMe** and nitrile **17-1-CN** substituted derivatives did not react in dry dichloromethane, these reactions were studied in dry acetonitrile. While the ester derivative **17-1-COOMe** gave an inseparable mixture of the plausible isomers, the nitrile **17-1-CN** gave the D-*galacto* configured chloroazidated derivative **17-2-CN** in good yield (50%). Similar reactivity was observed with the D-*arabino* configured glycals **17-5**, but transformation of the carbamoyl substituted derivative **17-5-CONH$_2$** resulted in the formation of chloroamidated by-product **17-8-CONH$_2$** (19%) in dry acetonitrile and formation of inseparable mixture was observed using dry dichloromethane. Inseparable mixture was formed in the case of methoxycarbonyl substituted *arabino* configured glycal **17-5-COOMe** in dry acetonitrile and no transformation was detected in dry dichloromethane. Nitrile derivative of D-*arabino* configured glycal **17-5-CN** reacted only in dry acetonitrile, and a mixture of D-*gluco* **17-6-CN** and D-*manno* **17-7-CN** isomers was isolated with D-*gluco* preferences (48%; ratio of the isomers is 10 : 7), which could be separated by preparative HPLC. The configuration of C-1 and C-2 centers was determined by measuring $^3J_{H\text{-}H}$ between H-2 and H-3 and $^3J_{H\text{-}C}$ coupling constants between H-2 and C of 1-*C* substituents (Scheme 17).

Bromoazidation reactions of D-*lyxo* configured 1-C-acceptor-substituted glycals **18-1** were performed with NBS/$TMSN_3$/$Yb(OTf)_3$ in dry acetonitrile or dichloromethane (Scheme 18).

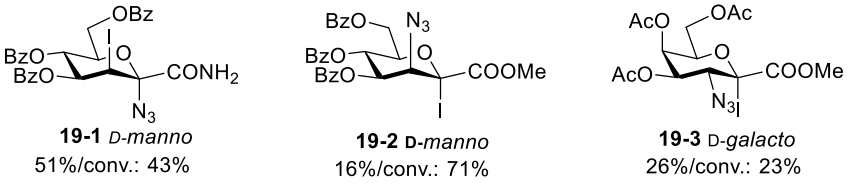


Scheme 18: Bromoazidation of D-*lyxo* configured 1-C-acceptor-substituted D-glycals

Carbamoyl substituted glycal **18-1-CONH2** reacted very fast in dry acetonitrile (10 mins), but the D-*galacto* configured product **18-2-CONH2** could be isolated only with low yield (11%). The reaction was slower in dry dichloromethane (2 h) and only the formation of regio- and stereoisomers could be detected, but their separation was unsuccessful. Slower reactions of methoxycarbonyl derivative **18-1-COOMe** were observed in dry acetonitrile (1.5 h; conv.: 100%) and dry dichloromethane (5.5 h, conv: 65%) and the D-*galacto* configured product **18-2-COOMe** was isolated in moderate or good yields (23% and 50%). In the case of total conversion in dry dichloromethane (168 h) a mixture of regio- and stereoisomers were isolated in good yields (59%; ratio of D-*galacto* and D-*talo** was 87 : 13). In the case of nitrile substituted glycal **18-1-CN**, slower reaction rates were observed in both solvents (dry ACN 24 h/ conv: 94% ; dry DCM 22 h/conv: 86%), and mixture of D-*galacto* **18-2-CN** and D-*talo* **18-4-CN** stereoisomers was isolated in moderate (31% in dry DCM) or good yields (50% in dry ACN). The ratios of the stereoisomers were 83 : 17 and 91 : 9, respectively, with D-*galacto* preferences.

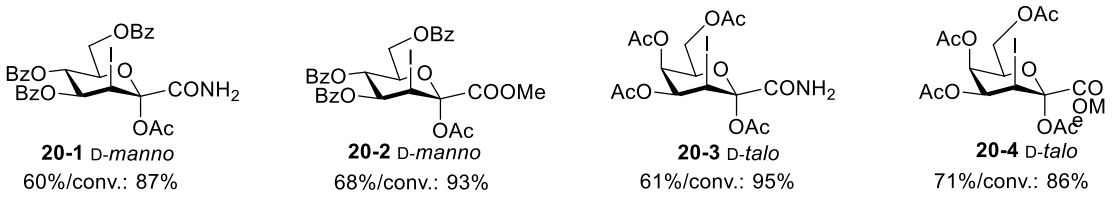
In the case of D-*arabino* configured *O*-perbenzoylated 1-C-acceptor-substituted glycal derivatives formation of a complex mixture of stereo/regioisomers and by-products was observed which could not be separated.

Iodoazidation was performed with $Me_3SI/PIDA/TMSN_3$ in dry acetonitrile under inert atmosphere. The desired product could be isolated only in three cases in low to moderate yields. While the transformation of D-*arabino* configured *O*-perbenzoylated carbamoyl ($CONH_2$) and methoxycarbonyl (COOMe) substituted glycals gave regioisomer D-*manno* configured products **19-1** and **19-2**, respectively, with axial position of substituents on C-2, the D-*lyxo* configured *O*-peracetylated methoxycarbonyl (COOMe) glycal gave D-*galacto* configured product **19-3** with azide in equatorial position on C-2. The carbamoyl ($CONH_2$) derivative of D-*lyxo* configured glycal gave an inseparable mixture of regio- and stereoisomers, while nitrile (CN) derivatives did not react (Scheme 19).



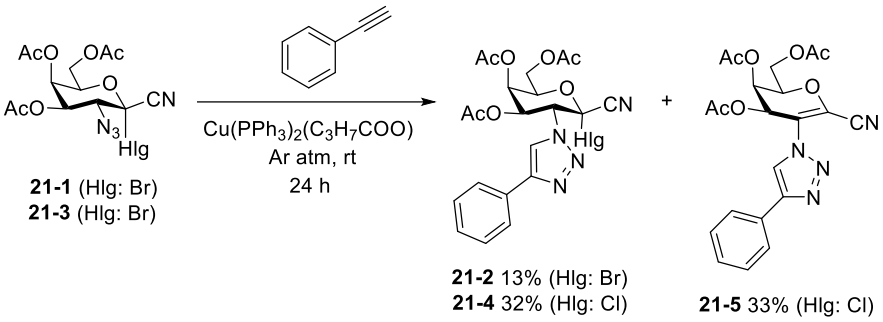
Scheme 19: Iodoazidation of 1-C-acceptor-substituted glycals

Acetoxyiodinations of D-*lyxo* and D-*galacto* configured *O*-peracylated-1-C-acceptor-substituted glycals were studied with $Me_3SI/PIDA/AcOH/Ar/r.t.$. While the nitrile substituted glycals did not react under these conditions the carbamoyl ($CONH_2$) and methoxycarbonyl (COOMe) substituted derivatives gave the corresponding 1-deoxy-2-iodo derivatives **20-1** - **20-4** in good yields (60%-71%) with axial position of iodine on C-2 (Scheme 20).



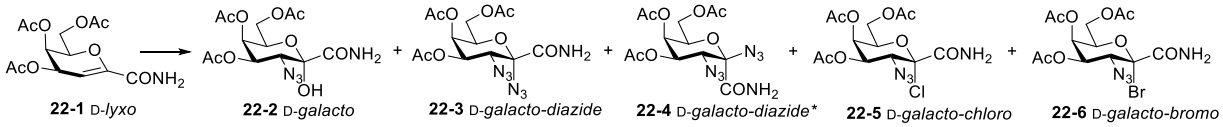
Scheme 20: Acetoxyiodinations of 1-C-acceptor-substituted glycals

Azide-alkyne click reaction of haloazidated compounds **21-1** and **21-3** were performed with phenylacetylene and the desired compounds **21-2** and **21-4** were isolated in low (13%) or moderate (32%) yields, a glycal – triazole derivative **21-5** was also isolated in moderate yield (33%) (Scheme 21). ***Haloazidation and azide-alkyne CuAAC reactions have been compiled in manuscripts to be submitted soon.***



Scheme 21: CuAAC reaction of haloazidated glycals

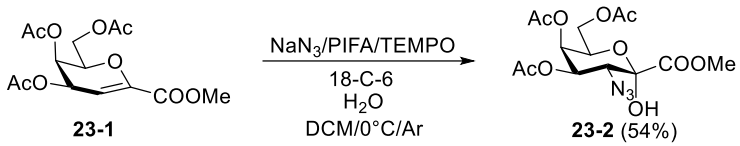
Hydroxyazidation of *O*-peracylated-1-C-acceptor-substituted glycals was studied using literature conditions ($TMSN_3$/PIFA/TEMPO/Bu_4NHSO_4 (50 equiv.) H_2O/dry DCM/0°C/Ar), which were ineffective for the transformation of our glycals, so an optimization of conditions was necessary. Using the original conditions, the formation of D-*galacto* configured hydroxyazide **22-2** and D-*galacto*-diazide **22-3** was observed in low yield (conv: 91%; yields: 24% and 18%, respectively). Using $BnEt_3NCl$ or Bu_4NBr, formation of haloazidated derivatives **22-5** and **22-6** as by-products was observed in low yields (13% and 19%) beside the hydroxy **22-2** (28% and 13%) and diazidated **22-3** (9% and 14%) and **22-4** (4% and 0%) compounds (Scheme 22).



Scheme 22: Optimization of hydroxyazidation of carbamoyl substituted D-*lyxo* configured glycal

The formation of haloazidated compounds was eliminated using crown-ether (18-C-6) as phase transfer catalyst. We also studied the effect of the azide sources ($TMSN_3$ or NaN_3), the amount of water (from 25 equiv. to 100 equiv.). The optimal conditions were the following: 3 equiv. NaN_3, 2 equiv. PIFA, 0.3 equiv. TEMPO, 0.2 equiv. 18-C-6 and 50 equiv. of H_2O. Using these conditions, the hydroxyazidated compound **22-2** could be isolated with 36% yield (conv: 100%) without the formation of any previously mentioned side-products. Hydroxyazidation of methoxycarbonylated D-*lyxo* configured glycal **23-1** was performed under these conditions, and

the desired product **23-2** was isolated in good yield (54%) (Scheme 23). ***These results have been compiled in manuscripts to be submitted soon.***



Scheme 23: Hydroxyazidation of methoxycarbonyl-substituted glycal

Addition of halogens to 1-C-substituted glycals under radical and ionic conditions

Additions of bromine and chlorine to *O*-peracylated 1-C-substituted (CN, COOMe, $CONH_2$) glycals were studied under ionic and radical conditions. The main products were the corresponding 2,3-*trans*-diaxial 2,3-dibromo-heptonic acid derivatives. Bromination of the *O*-peracetylated heptenonitrile and all chlorinations proved selective towards the 2-axial-3-equatorial 2,3-dihalogenoheptonic acid derivatives. Silver triflate promoted glycosylation of methanol was successful with each 2,3-*trans*-diaxial 2,3-dibromo-heptonic acid derivative, however, several attempted nucleophilic substitution and elimination reactions gave the parent glycal only.
Publication: *Carbohydr. Res.* 2021, *504*, 108292.
https://doi.org/10.1016/j.carres.2021.108292

Study of the Ferrier rearrangement of 1-C-acceptor-substituted glycals

The reaction of 1-C-substituted glycal derivatives with several O-, N-, S- and C-nucleophiles in the presence of Lewis acids (BF_3 x OEt, $TiCl_4$, BBr_3, etc.) was carried out and we found that with alcohols or NaN_3 the reactions took place at the C-3 carbon atom of the pyranose ring (allylic substitution), but in the case of benzylthiol the corresponding 2,3-unsaturated thioglycoside was formed (Ferrier rearrangement).
Publication: *Carbohydr. Res.*, 2022, *519*, 108582.
https://doi.org/10.1016/j.carres.2022.108582

Further unsuccessful transformations

Several other, planned transformations were studied during this research, which were unsuccessful, any transformation or the formation of the desired products were not detected. These transformations were the following: *Buchwald-Hartwig coupling* reaction of 2-halo-glycals; *Paterno-Büchi* reactions of *exo*-glycals with oxo compounds under irradiation with UV light; perfluoroalkylation and trifluoromethylsulphanylation of glycals and 1-C-substituted-glycals under photocatalytic condition, irradiation with blue LED.

Summary

In the field of metal-catalyzed and metal-free coupling reactions of anhydro-aldose tosylhydrazones successful C-C and C-N coupling reactions have been reported, and C-N coupling reactions were extended to aromatic *N*-tosylhydrazones. However, our efforts to carry

out similar couplings with aldono-lactone tosylhydrazones almost completely failed. We achieved considerable success during the transformations of *exo*-glycals and 1-C-subsituted *exo*-glycals, however the structure elucidation of the products often presented us with challenges and took considerable time. Despite the difficulties, we have achieved many results and synthesized a large number of new molecules, which are significantly expanded the toolkit of carbohydrate chemistry. Investigations are continued in this area since it is a rather understudied area of carbohydrate chemistry with a promise of unique results.
Besides the 8 publications in the report, 2 manuscripts have been submitted for publication and 6 other papers are in preparation as indicated in the relevant parts of this report. The realization of the project resulted in 2 PhD dissertations (1 of this is in preparation (Á. Homolya) and will be defended in 2023), 6 MSc and 22 BSc theses.

Vágvölgyiné Dr. Tóth Marietta
vezető kutató