Short thesis for the degree of Doctor of Philosophy (PhD)

Study of the reactivity of glycal derivatives: addition reactions and palladium catalyzed coupling reactions

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1. Introduction and objectives

Carbohydrates are essential compounds for living organisms, they play a crucial role in the biological systems. Due to their structural diversity carbohydrates are the most numerous class of organic compounds in nature, and their biological functions are also extremely multifaceted.

Their widely applicable representatives are the glycals, which contain a double bond between the C-1 and C-2 atoms of the sugar ring, whose unsaturation provides an outstanding variability in the field of chemical transformations.

My research work focused on the functionalization of the double bond in a narrow class of glycals containing electron withdrawing groups on the C-1 atom. We planned to study the reactivity of these compounds in addition reactions such as haloazidation and hydroxyazidation and to examine the effect of the substrate structure and the reaction conditions on the regio- and stereoselectivities of the transformations.

We also planned the synthesis of 2-iodoglycal derivatives and a study of their Pd-catalyzed Sonogashira- and Heck coupling reactions. 2-Ethynylglycals, to be obtained from the Sonogashira reactions, were planned to be reacted with various azide derivatives under CuAAc conditions.

2. The applied methods

During our research work a wide range of methods of preparative organic chemistry and separation techniques were used. The reactions were monitored by TLC and the crude products were purified by column chromatography or crystallization. In some cases, when the isomers were hard to separate, preparative HPLC was applied. The structural elucidation of the products was conducted using 1D and 2D NMR experiments, IR and MS

measurements. To complete the characterization of the synthesized compound optical rotation was also measured.

3. New results of the thesis

3.1. Study of the addition reactions of 1-C-substituted glycal derivatives

3.1.1. Study of the haloazidation reaction of 1-C-substituted glycal derivatives

The haloazidation of compounds **56-61** was studied in detail as to the quality of the halogen, the reaction conditions, and the substrate. The conditions of iodoazidation were optimized using glycal **56**, and the best conditions were determined as follows: Me_3SI/PIDA/$TMSN_3$/dry ACN/0 °C → rt/Ar.

During the iodoazidation of D-*lyxo* configured 1-carbamoyl glycal **56** (**Table 1**, **entry 1**) the starting material was consumed in 48 hours, but an inseparable mixture was formed.

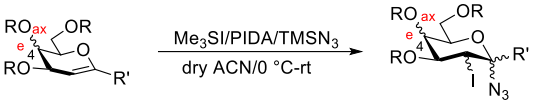
The transformation was extended to D-*lyxo* configured 1-methoxycarbonyl glycal **57** and 1-cyano substituted derivative **58**. While from the reaction of compound **57** the iodoazide **233** was isolated with low conversion and in low yield (**Table 1**, **entry 2**), in the case of glycal **58** no reaction was observed (**Table 1**, **entry 3**).

The transformation of D-*arabino* configured glycals **59-61** showed the same tendency. The only difference was that, contrary to the observations with D-*lyxo* configured glycal **56**, from the reaction of 1-carbamoyl glycal **59** the iodoazide **234** was isolated in pure state **56** (**Table 1**, **entry 4-6**).

The bromoazidation reactions were optimized with the D-*lyxo* 1-carbamoyl glycal **56**, and the NBS/$TMSN_3$/$Yb(OTf)_3$ reagent system was found to be optimal. The reactions of glycal

derivatives **56-61** were carried out using acetonitrile and dichloromethane, too (**Table 2**).

Table 1: Iodoazidation of 1-C-substituted glycal derivatives **56-61** using Me_3SI/PIDA iodine source

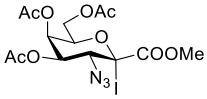
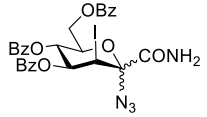
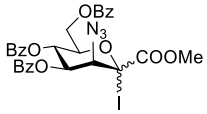


56-61

56-58 D-*lyxo*, 4-OR ax., R = Ac
59-61 D-*arabino*, 4-OR e., R = Bz

232

R' = CN, COOMe, $CONH_2$

No.	Glycal	R'	Time (h)	Product [conversion[a] (%)/ yield[b] (%)]
1	**56**	$CONH_2$	48	complex product mixture
2	**57**	COOMe	192	 **233** (26/23)
3	**58**	CN	168	no transformation
4	**59**	$CONH_2$	168	 **234** (43/51)
5	**60**	COOMe	240	 **235** (71/16)
6	**61**	CN	168	no transformation

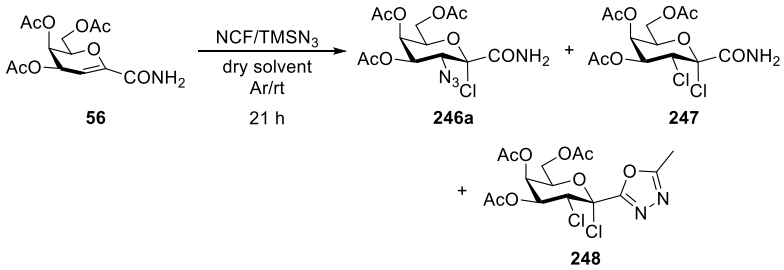
[a]Unreacted starting material was collected from the purification. [b]The yield was corrected with the conversion: [yield(%) / conversion(%)] × 100.

All the six glycals could be reacted under these conditions, but the bromoazidation of the D-*lyxo* configured glycals showed higher selectivity than the D-*arabino* ones. In the reaction of D-*lyxo* glycals **56-58** compounds **237**-**240** were formed (**Table 2**), and in all cases the 1-axial-2-equatorial bromoazide **237** was the main product. The 1-carbamoyl derivative **56** was the most reactive with the lowest selectivity, and 1-cyano compound **58** was found to be the least reactive.

The bromoazidations of D-*arabino* configured glycals were less selective, and only inseparable mixtures of isomers could be obtained from the reactions.

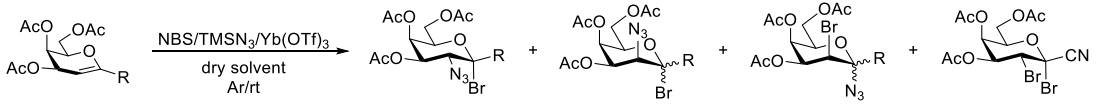
The chloroazidation was performed with NCF/$TMSN_3$ reagents, and the applied solvents (dry ACN or DCM) were selected in preliminary experiments with D-*lyxo* glycal **56**.

When the glycal **56** was reacted in acetonitrile, the formation of 1,3,4-oxadiazole **248** was observed (30%) (**Scheme 1**), however in dichloromethane, chloroazide **246a** and dichloro compound **247** were isolated as an inseparable mixture (**246a** : **247** = 91 : 9) with 54%.



Scheme 1: Chloroazidation of D-*lyxo* glycal **56**

Table 2: Ytterbium-triflate catalyzed bromoazidation of D-*lyxo* configured glycals



56-58

237a R = $CONH_2$
237b R = COOMe
237c R = CN

238a R = $CONH_2$
238b R = COOMe
238c R = CN

239a R = $CONH_2$
239b R = COOMe
239c R = CN

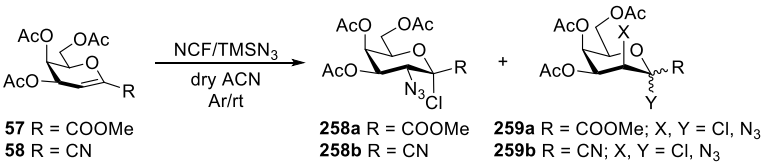
240

No.	Glycal	R	Solvent	Time (h)	Conv. (%)[a]	Product (yield, %)[b]	Product ratio[c]
1	**56**	$CONH_2$	DCM	2	100	complex mixture	-
2			ACN	0,17	100	**237a** (11)[d]	-
3	**57**	COOMe	DCM	5,5	65	**237b** (50)[e]	-
4				168	100	**237b** + **239b** (60)	**237b** : **239b** = 87 : 13
5			ACN	1,5	100	**237b** (23)[f]	-
6	**58**	CN	DCM	168	100	**237c** (35) + **240** (6)	**237c** : **240** = 83 : 17
7			ACN	20	83	**237c** + **238c** (44)[e,g]	**237c** : **238c** = 81 : 19

[a]Unreacted starting material was collected from the purification. [b]Isolated yield. [c]Calculated from the ^{1}H NMR spectra of the mixture. [d]The product is contaminated with a small amount of succinimide. [e]The yield was corrected with the conversion: [yield (%) / conversion (%)] × 100. [f]The yield of the isolated pure product. [g]The mixture could not be separated completely, but bromoazide **237c** could be isolated in a pure form in 20% corrected yield.

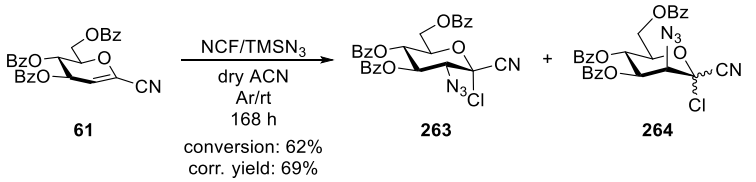
The D-*lyxo* configured derivatives **57**, **58** were reactive only in acetonitrile (**Scheme 2.**), and mixtures of D-*galacto* (**258a,b**) and D-*talo* (**259a,b**) configured chloroazides were formed, which could be partially separated.

From the reaction of glycal **57** a mixture of isomers **258a** and **259a** (**258a** : **259a** = 79 : 21) was isolated in low corrected yield (29%), while in the chloroazidation of 1-cyano glycal **58** a partially separable mixture of isomers **258b** and **259b** was formed in good corrected yield (78%, **258b** : **259b** = 82 : 18).



Scheme 2: Chloroazidation of D-*lyxo* configured 1-methoxycarbonyl- and 1-cyano glycals

During the chloroazidation of D-*arabino* configured glycals 1-cyano derivative **61** gave a mixture of the desired chloroazides **263**, **264** in good yield (**Scheme 3**), however in the case of glycals **59** and **60**, complex mixtures of isomers were formed.

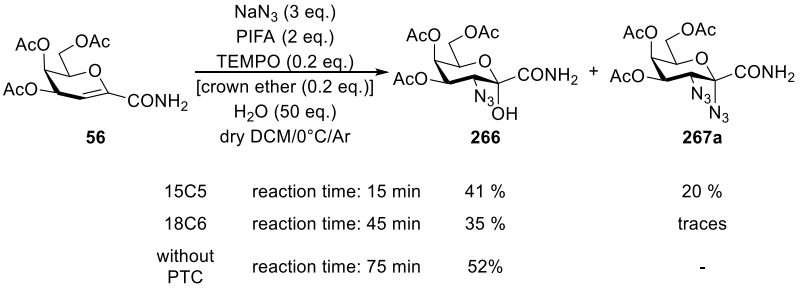


Scheme 3: Chloroazidation of D-*arabino* glycal **61**

The structural elucidation was performed by using a combination of IR, MS and NMR techniques, and by comparing the spectroscopic data of the new compounds with literature examples. In some cases (**237c**, **246a**, **258b**) chemical transformations were carried out to prove the assumed structures.

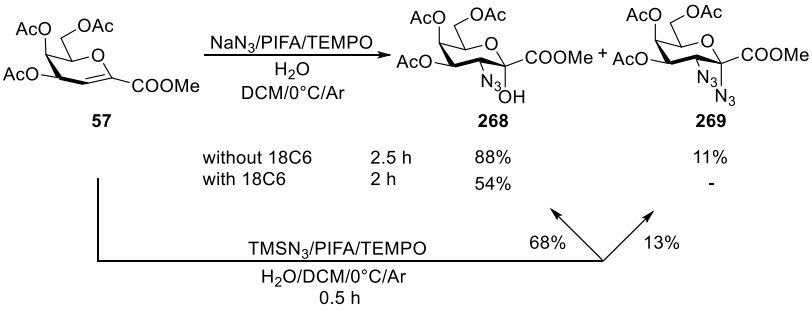
3.1.2. Study of the hydroxyazidation reaction of 1-C-substituted glycal derivatives

For hydroxyazidations an optimization was carried out with 1-carbamoyl substituted D-*lyxo* glycal **56**.



Scheme 4: Hydroxyazidation of glycal **56** in the presence of PTC and without PTC

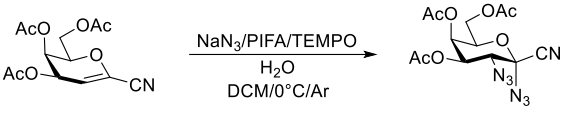
Under the optimized conditions – without PTC – hydroxyazide **266** was isolated in moderate yield (**Scheme 4**), which was better than in the presence of PTC.



Scheme 5: Hydroxyazidation of 1-methoxycarbonyl glycal **57**

A similar tendency was observed in the case of 1-methoxycarbonyl glycal **57** (**Scheme 5**). Under the optimized conditions (without PTC) hydroxyazide **268** was formed with

better yield (88%, 68%) than in the presence of PTC (54%) (**Scheme 5**).

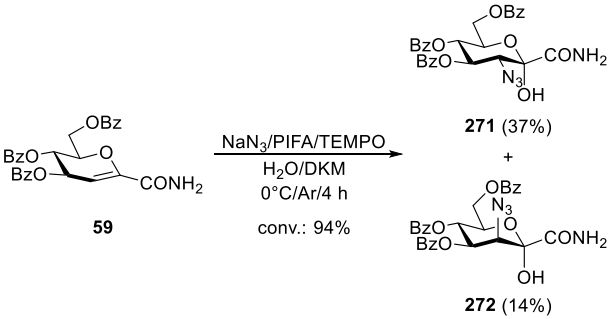


without 18C6: conv.: 40% corrected yield: 96%
with 18C6: conv.: 40% corrected yield: 32%

Scheme 6: Hydroxyazidation of 1-cyano glycal **58**

The hydroxyazidation of 1-cyano glycal **58** was also studied with or without PTC (**Scheme 6**). Although the rate of the reactions was similar, the 1,2-*cis*-diazide **270** was isolated in excellent yield without PTC, and only in low yield with PTC.

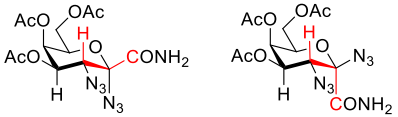
The hydroxyazidation of D-*arabino* configured 1-carbamoyl glycal **59** provided hydroxyazide derivatives with D-*gluco* (**271**) and D-*manno* (**272**) configuration in moderate and low yields, respectively (**Scheme 7**).



Scheme 7: Hydroxyazidation of D-*arabino* configured glycal **59**

In the reaction of 1-methoxycarbonyl substituted D-*arabino* glycal **60** an inseparable product mixture was formed, and no transformation was observed with 1-cyano glycal **61**.

The structures were elucidated by using a combination of IR, MS and NMR techniques. One of the biggest challenges of the structural elucidation was the determination of the anomeric configuration, which was based on a comparison of the heteronuclear three-bond coupling constants ($^3J_{H\text{-}3,C\text{-}1}$) of hydroxyazides and diazide anomers **267a,b** (**Scheme 8**).

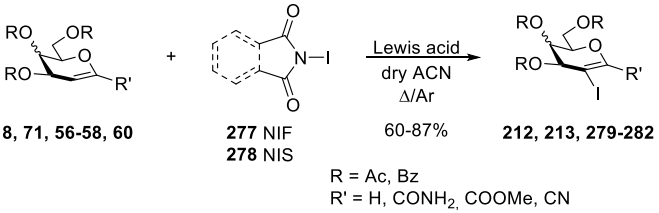


Scheme 8: Heteronuclear three-bond coupling constants between H-3 and C-1 atoms

3.2. Study of the palladium catalyzed coupling reactions of 2-iodoglycals and 2-iodo-1-C-substituted glycal derivatives

3.2.1. Synthesis of 2-iodoglycals and 2-iodo-1-C-substituted glycals

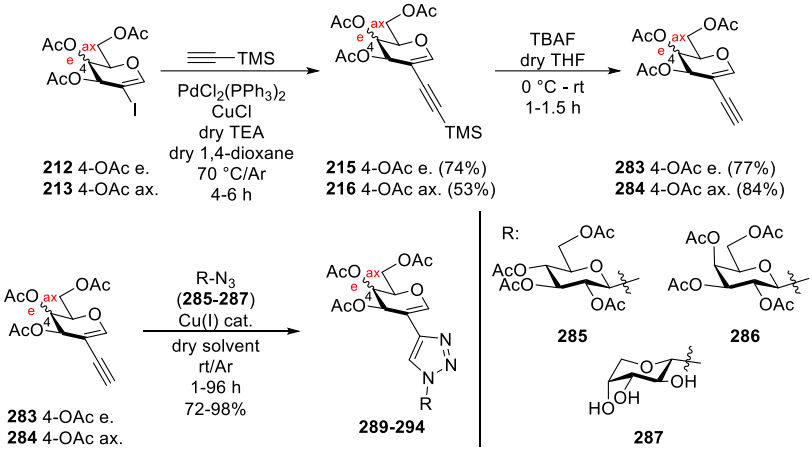
We have developed a procedure to synthesize 2-iodo-1-C-substituted glycals (**279-282**) using *N*-iodoimides (**277**, **278**) as iodine source and $AgNO_3$ or TMSOTf as promoter (**Scheme 9**). From these reactions the desired compounds could be obtained in moderate to good yields. The synthesis of the 2-iodoglycals (**212**, **213**) was carried out based on a literature procedure.



Scheme 9: The synthesis of iodoglycals starting from glycals

3.2.2. Study of the Sonogashira cross-coupling reaction of 2-iodoglycals and 2-iodo-1-C-substituted glycals

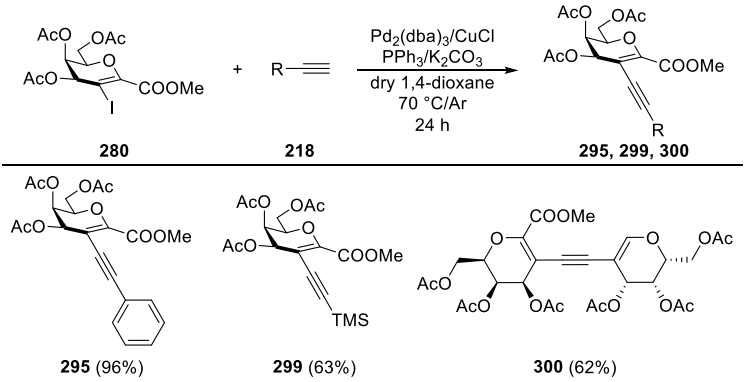
Sonogashira cross-coupling reaction was used for the synthesis of 2-ethynylglycal derivatives (**283**, **284**), which were reacted with glycosyl azides **285-287** under CuAAC conditions to give 1,4-disubstituted-1,2,3-triazoles **289-294** in good and excellent yields (**Scheme 10**).



Scheme 10: The synthesis of 2-ethynylglycals and their CuAAC reactions

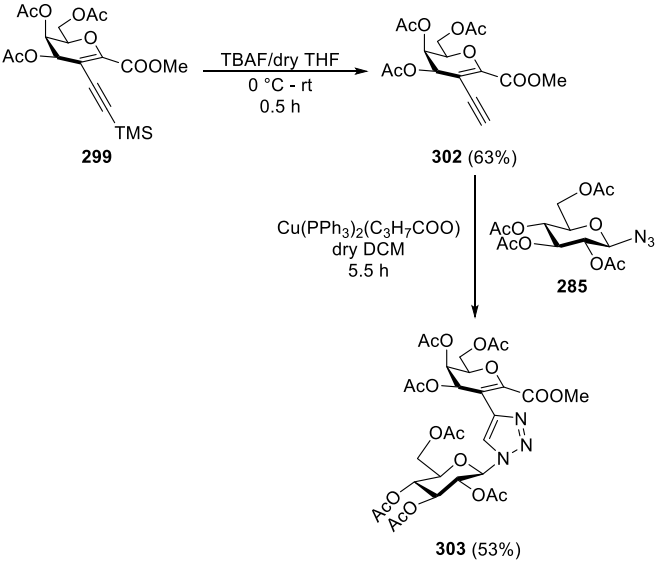
The Sonogashira cross-coupling of the 2-iodo-1-C-substituted glycals was optimized for the reaction of the 1-methoxycarbonyl glycal **280** with phenylacetylene (**218**, R = Ph) (**Scheme 11**).

The effect of the base, the catalyst system and the solvent on the outcome of the reactions was investigated, and the optimal conditions were determined as shown in **Scheme 11**.



Scheme 11: Sonogashira cross-coupling reaction of iodoglycal **280** with different terminal alkynes

Under these conditions iodoglycal **280** was reacted with trimethylsilyl acetylene and 2-ethynylglycal **284**, too (**Scheme 11**).



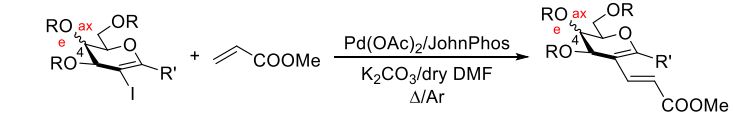
Scheme 12: The synthesis of 1,4-disubstituted triazole starting from 1-C-substituted glycal

From the coupling reactions the disubstituted acetylene derivatives **295**, **299**, **300** were isolated in moderate to excellent yields (**Scheme 11**). Silyl protected **299** was used to synthesize 1,4-disubstituted triazole **303** (**Scheme 12**).

3.2.3. Study of the Heck reaction of 2-iodo-1-C-substituted glycal derivatives

The Heck reaction of the 2-iodo-1-C-substituted glycals was optimized for the reaction of 1-methoxycarbonyl derivative **280** with methyl acrylate. The coupled product **304** was isolated from the reaction mixture in good yield. During the optimization process the effect of the base, the catalyst system and the solvent was investigated, and the optimal conditions were determined (**Table 3**, **entry 1**).

Table 3: Heck reaction of iodoglycals **279-282**



279-281 D-*lixo*, 4-OR ax. **224** R' = $CONH_2$, COOMe, CN **304, 305**
282 D-*arabino*, 4-OR e.

No.	Glycal	R	R'	T (°C)	Time (h)	Product (yield, %)
1	**280**	Ac	COOMe	90	0.33	**304** (82)
2	**282**	Bz	COOMe	90	0.33	**305** (49)
3	**279**	Ac	$CONH_2$	110	4.5	-[a]
4	**281**	Ac	CN	90	0.25	-

[a]According to the TLC and NMR measurements, only dehalogenation happened.

The coupling reaction was also carried out using D-*lyxo* configured 1-carbamoyl (**279**) and 1-cyano (**281**) glycals, and D-

arabino configured 1-methoxycarbonyl glycal **282** (**Table 3**). Among these substrates, the desired coupled product was isolated in moderate yield only from the reaction with iodoglycal **282** (**Table 3, entry 2**).

4. Possible applications

During our research several bifunctional monosaccharide derivatives, 2-alkenyl- and 2-alkynylglycals and 1,4-disubstituted triazoles were synthesized. These compounds could be possible starting materials in the synthesis of compounds with more complex, carbohydrate containing structures.

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Registry number: DEENK/343/2024.PL
Subject: PhD Publication List

Candidate: Ágnes Homolya
Doctoral School: Doctoral School of Chemistry
MTMT ID: 10095253

List of publications related to the dissertation

Foreign language scientific articles in international journals (2)

1. Juhász-Tóth, É., Malecz, Á. S., Tóth, M., **Homolya, Á.**, Kaszás, T., Somsák, L., Juhász, L.: 2-Iodo-1-C-acceptor-substituted glycals: synthesis and transformation into 1,2-C,Cdisubstituted glycals via Suzuki-Miyaura coupling reaction.
   New J. Chem. 47 (42), 19376-19388, 2023. ISSN: 1144-0546.
   DOI: http://dx.doi.org/10.1039/D3NJ03119E
   IF: 3.3 (2022)
2. **Homolya, Á.**, Jedlóczki, I., Ábrahám, A., Somsák, L., Tóth, M., Juhász, L.: Behaviour of some 1-C-acceptor-substituted glycals under azidohydroxylation conditions.
   Carbohydr. Res. 529, 1-12, 2023. ISSN: 0008-6215.
   DOI: http://dx.doi.org/10.1016/j.carres.2023.108825
   IF: 3.1 (2022)

Total IF of journals (all publications): 6,4
Total IF of journals (publications related to the dissertation): 6,4

The Candidate's publication data submitted to the iDEa Tudóstér have been validated by DEENK on the basis of the Journal Citation Report (Impact Factor) database.

10 June, 2024

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Presentations and poster presentations related to the dissertation

Presentations

1. **Homolya Ágnes**, Csomay Eszter, Peleskei Zsófia, Juhász László; 2-Jódglikálok és 2-jód 1-C-akceptor-szubsztituált glikálok Sonogashira és Heck kapcsolási reakciói; BME Szerves-és Gyógyszerkémiai Nap, Budapest, 2023. június 30.
2. **Homolya Ágnes**, Peleskei Zsófia, Csomay Eszter, Juhász László; 2-jódglikálok palládium katalizált keresztkapcsolási reakciói; MTA Heterociklusos és Elemorganikus Kémiai Munkabizottság ülése, Balatonszemes, 2023. május 31-június 2.
3. **Ágnes Homolya**, Eszter Csomay, Zsófia Peleskei, Kristóf Kovács, Éva Juhász-Tóth, Marietta Tóth, László Somsák, László Juhász; Cross coupling reactions in glycal chemistry: Sonogashira and Heck coupling of 2-iodo-1-C-substituted glycals; Annual meeting of the Working Committee for Carbohydrates, Nucleic Acids and Antibiotics of the Hungarian Academy of Sciences; Mátrafüred, Hungary, 2023. május 24-26.
4. **Homolya Ágnes**, Jedlóczki Ivett, Somsák László, Tóth Marietta, Juhász László; Telítetlen szénhidrátszármazékok haloazidálása; Vegyészkonferencia 2022, Eger, 2022. június 15-17.
5. **Homolya Ágnes**, Csomay Eszter, Tóth Éva, Tóth Marietta, Somsák László, Juhász László; 2-jód 1-C-szubsztituált glikálok Sonogashira és Heck kapcsolási reakciói; MTA Szénhidrát, Nukleinsav és Antibiotikumkémiai Munkabizottság 2022. évi ülés és szakmai előadónap, 2022. május 27. (online)
6. **Homolya Ágnes**, Tóth Éva, Malecz Ádám Szilárd, Petróczi Ferenc Dániel, Csomay Eszter, Tóth Marietta, Somsák László,

Juhász László; 2-jód 1-C-szubsztituált glikálok Sonogashira, Heck és Suzuki-Miyaura kapcsolási reakciói; MTA Heterociklusos és Elemorganikus Kémiai Munkabizottság ülése, Balatonszemes, 2022. május 23-25.

7. **Homolya Ágnes**, Peleskei Zsófia, Jedlóczki Ivett, Somsák László, Juhász László; Haloazidálás: 1-C szubsztituált glikálok vicinális bifunkcionalizálása; II. FKF Szimpózium; 2021. június 16-18. (online)
8. **Homolya Ágnes**, Peleskei Zsófia, Jedlóczki Ivett, Somsák László, Vágvölgyiné Tóth Marietta, Juhász László; 1-C szubsztituált glikálok bifunkcionalizálása – haloazidált származékok előállítása; MTA Szénhidrát, Nukleinsav és Antibiotikumkémiai Munkabizottság 2021. évi ülés és szakmai előadónap; 2021. június 14. (online)
9. **Homolya Ágnes**, Peleskei Zsófia, Somsák László, Juhász László; 1-C szubsztituált glikál származékok haloazidálási reakcióinak tanulmányozása; XXIV. Tavaszi Szél Konferencia; 2021. május 28-30. (online)

Poster presentations

10. **Ágnes Homolya,** Eszter Csomay, Zsófia Peleskei, Éva Juhász-Tóth, Marietta Tóth, László Somsák, László Juhász; Palladium catalyzed Sonogashira and Heck coupling reactions of 2-iodo-1-C-substituted glycals; 21th European Carbohydrate Symposium; Paris, France, July 9-13, 2023.
11. **Ágnes Homolya**, Eszter Csomay, Éva Juhász-Tóth, László Somsák, Marietta Tóth, László Juhász; Palladium catalysed cross-coupling reactions of 2-iodo 1-C-substituted glycals: Heck and Sonogashira reactions; Debrecen Colloquium on Carbohydrates 2020 in 2022, Debrecen, August 24-27, 2022.
12. **Ágnes Homolya**, Zsófia Peleskei, Ivett Jedlóczki, László Somsák, Marietta Tóth, László Juhász; Functionalization of

1-C-substituted glycal derivatives by addition reactions; Debrecen Colloquium on Carbohydrates 2020 in 2022, Debrecen, August 24-27, 2022.

13. Csomay Eszter, **Homolya Ágnes**, Juhász-Tóth Éva, Somsák László, Tóth Marietta, Juhász László; 2-jód 1-C-szubsztituált glikálok palládium katalizált kapcsolási reakciói; Vegyészkonferencia 2022, Eger, 2022. június 15-17.
14. Jedlóczki Ivett, **Homolya Ágnes**, Somsák László, Tóth Marietta, Juhász László; 1-C-szubsztituált glikál származékok hidroxiazidálási reakcióinak tanulmányozása; Vegyészkonferencia 2022, Eger, 2022. június 15-17.
15. Peleskei Zsófia, **Homolya Ágnes**, Somsák László, Tóth Marietta, Juhász László; 1-C-szubsztituált glikálok itterbium-triflát katalizált brómazidálása – szintézis és szerkezetvizsgálat; Vegyészkonferencia 2022, Eger, 2022. június 15-17.

Other presentations, poster presentations not related to the dissertation

1. **Ágnes Homolya**, Tímea Kaszás, Bence Szakács, Tekla Blága, Kyle Doherty, Trinidad Velasco-Torrijos, Hina Shafique, Zoárd Ecsedi, Éva Juhász-Tóth, László Juhász, Ulf J. Nilsson, László Somsák, Marietta Tóth; Synthesis of potentially biologically active carbohydrates: transformation of anhydro-aldose oximes; 21th European Carbohydrate Symposium; Paris, France, July 9-13, 2023.
2. Nawar Ahmad, **Ágnes Homolya**, Mihály Herczeg, Anikó Borbás; Synthesis of isochroman-sugar hybrids by Oxa-Pictet-Spengler cyclizations; Annual meeting of the Working Committee for Carbohydrates, Nucleic Acids and Antibiotics of the Hungarian Academy of Sciences; Mátrafüred, Hungary, 2023. május 24-26.

3. László Juhász, Éva Juhász-Tóth, **Ágnes Homolya**, László Somsák; Haloamination of Glycal Derivatives; 20th EUROCARB; Leiden, Nederland, June 30. – July 4, 2019.
4. Juhászné Tóth Éva, **Homolya Ágnes**, Juhász László, Somsák László; Glikál származékok haloaminálási reakciói; MKE Vegyészkonferencia 2019; Eger, 2019. június 24-26.
5. Éva Juhász-Tóth, **Ágnes Homolya**, László Juhász, László Somsák; Haloamination - new functionalization of glycal derivatives; International Workshop on Chemistry and Chemical Biology of Carbohydrates, Nucleic Acids and Antibiotics; Mátrafüred, Hungary, 2019. május 22-24.
6. **Homolya Ágnes**, Juhász László, Somsák László; 1-C szubsztituált glikál származékok átalakításainak vizsgálata; I. FKF Szimpózium; Debrecen, 2019. április 3-5.
7. Illyés Tünde Zita, **Homolya Ágnes**, Juhász László, Somsák László, Batta Gyula; Egy "egyszerű" monoszacharid konformációjának és konfigurációjának elemzése; Magyar NMR Munkabizottság előadóülése; Balatonszemes, 2018. május 24-25.
8. **Ágnes Homolya**, Mária Polyák, Attila Mándi, Tünde Zita Illyés, Gyula Batta, László Juhász, László Somsák; Transformations of 1-C substituted glycal derivatives; International Workshop on Chemistry and Chemical Biology of Carbohydrates, Nucleic Acids and Antibiotics; Mátrafüred, Hungary, 2018. május 23-25.
9. László Somsák, Mária Polyák, László Lázár, **Ágnes Homolya**, László Juhász; Study of radical-mediated transformations of 1-C substituted glycals; 19th European Carbohydrate Symposium; Barcelona, Spain, July 2-6, 2017.
10. Polyák Mária, Lázár László, **Homolya Ágnes**, Juhász László, Somsák László; 1-C szubsztituált glikálok gyökös

reakcióinak tanulmányozása; MKE Vegyészkonferencia 2017; Hajdúszoboszló, 2017. június 19-21.