Heterocyclic Letters
Vol. 15| No.1|205-216|Nov-Jan|2025
ISSN : (print) 2231–3087 / (online) 2230-9632
CODEN: HLEEAI
http://heteroletters.org

SWEET SCIENCE: UNVEILING BIOLOGICALLY ACTIVE SUGAR-BASED CHIRAL ISOXAZOLES

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Abstract: In the vast realm of organic chemistry, the isoxazole ring system stands as a remarkable and versatile scaffold, captivating the attention of scientists and researchers alike. Comprising a five-membered heterocyclic ring with oxygen and nitrogen atoms at adjacent positions, isoxazoles possess unique structural features that bestow them with diverse chemical reactivity and significant biological relevance. Their intriguing properties and applications have rendered them indispensable in the fields of medicinal chemistry, pharmacology, and materials science. However, many biological processes rely on the specific recognition of molecules by enzymes, receptors, and other biomolecules. Chirality allows for a high degree of specificity in these interactions. Enantiomers, despite having the same chemical formula, often exhibit vastly different biological activities. This selectivity is crucial for functions such as enzyme-substrate interactions, signal transduction, and drug-receptor binding. Chirality is a critical consideration in drug design and development. Many drugs are chiral compounds, and their biological activity often depends on the specific enantiomer. In some cases, one enantiomer may provide the desired therapeutic effect, while the other may have adverse effects or no effect at all. Separating and using the correct enantiomer is essential for drug safety and efficacy. Recognizing the paramount significance of chirality, this review article centers its spotlight on carbohydrates—an abundant and versatile gift from nature. We delve into their remarkable role as chiral templates in crafting isoxazole conjugate with profound therapeutic implications.

Keywords: isoxazole, chirality, carbohydrates, 1,3-dipolar cycloaddition

Introduction:

Carbohydrate conjugates refer to molecules in which carbohydrates, such as sugars, are chemically linked or conjugated to other molecules, typically proteins, peptides, lipids, or small organic molecules. These conjugates have diverse applications in biology, medicine, and materials science. The most common types of carbohydrate conjugates include glycoprotein and glycolipids, glycosaminoglycans (GAGs), antibody-drug conjugates (ADCs), vaccines, and biomarkers. Moreover, the influence of carbohydrate conjugates extends beyond the realms of medicine. They are pivotal players in the captivating fields of materials science and chemical biology. Carbohydrates, when cleverly harnessed, become versatile components, woven into polymers and other materials to give life to functional

wonders. These wonders find their place in the world of tissue engineering, precise drug delivery, and the enchanting universe of biomaterials. Carbohydrate conjugates emerge as indispensable tools, illuminating the mysteries of biological processes where glycan-protein interactions, deciphering the elegant patterns of glycosylation, and unraveling the enigma of carbohydrate-related diseases.

Tailoring carbohydrates with small heterocyclic scaffolds has given rise to an indispensable class of glycoconjugates, a treasure trove of compounds brimming with a myriad of captivating biological activities. A literature review shows that a wide range of carbohydrate-based azoles and triazoles, as well as their nucleoside analogs, such as ribavirin and tiazofurins, are being developed as prominent antiviral and anticancer drug candidates.

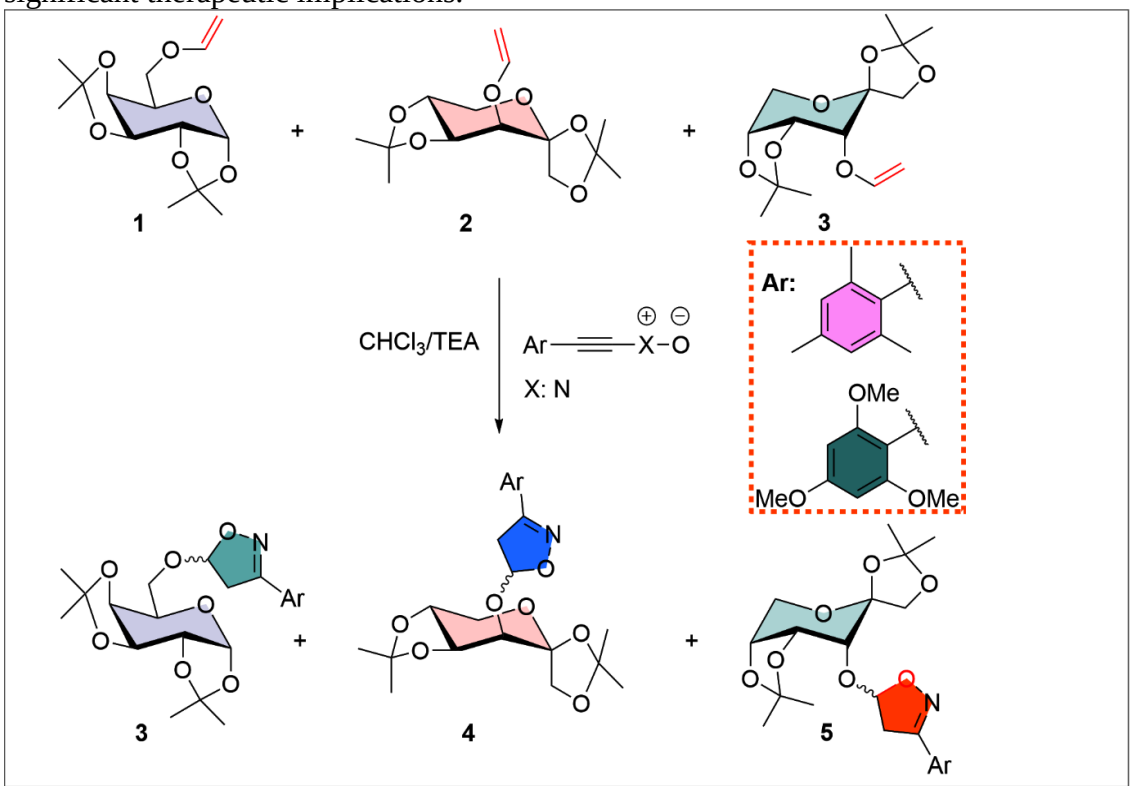
1,3-Dipolar cycloaddition is a fundamental synthetic method in organic chemistry, involving the reaction between a 1,3-dipole and a dipolarophile to form a cyclic product. This reaction is characterized by its regio- and stereoselectivity, making it a powerful tool for the construction of complex molecular architectures. Rolf Huisgen's a German Chemist first discovered the 1,3-dipolar cycloaddition in the mid-20th century. His journey towards the discovery of 1,3-dipolar cycloaddition began in the late 1940s when he started investigating the reactivity of nitrogen-containing compounds, particularly azides. Azides were known to undergo various reactions, but their behavior in cycloaddition reactions remained unexplored. In 1953, Huisgen published his seminal paper titled "1.3-Dipolare Cycloadditionen, I. Kinetik des Additionen von Cycloadditionen an Dienophile" (1,3-Dipolar cycloadditions, I. Kinetics of the addition of cycloadditions to dienophiles), where he reported the discovery and detailed study of what later became known as the Huisgen 1,3-dipolar cycloaddition. In this work, Huisgen demonstrated that organic azides could react with alkynes to form 1,2,3-triazoles, marking the first systematic exploration of 1,3-dipolar cycloaddition reactions. The 1,3-dipolar cycloaddition reaction has found extensive applications in the synthesis of isoxazole derivatives, which are important heterocyclic compounds with various biological activities and synthetic utility. The construction of the isoxazole ring system through 1,3-dipolar cycloaddition offers a straightforward and efficient route to access diverse isoxazole-containing compounds. Here's a general outline of the application of 1,3-dipolar cycloaddition in the synthesis of isoxazoles: (i) The synthesis of the 1,3-dipole, typically a nitrile oxide or an azomethine ylide, is the initial step. This can be achieved by various methods, such as oxidation of hydroxamates or hydroxylamines for nitrile oxide formation, or condensation of hydroxylamine derivatives with carbonyl compounds for azomethine ylide generation, (ii) The generated 1,3-dipole then undergoes a 1,3-dipolar cycloaddition reaction with an appropriate dipolarophile, often an alkene or an alkyne, to form the isoxazole ring system. The dipolarophile usually contains a functional group that can undergo further manipulation or modification to introduce desired substituents, (ii) After the formation of the isoxazole ring, the resulting cycloaddition product can be further functionalized or derivatized to introduce additional functionalities or structural diversity. This step allows for the synthesis of a wide range of isoxazole derivatives with tailored properties for specific applications, (iii) Isoxazole derivatives obtained through 1,3-dipolar cycloaddition have diverse applications in medicinal chemistry, agrochemicals, and materials science. Many isoxazole-containing compounds exhibit interesting biological activities, including antimicrobial, anticancer, antiviral, and anti-inflammatory properties, making them valuable targets for drug discovery and development, (iv) One classic example of the application of 1,3-dipolar cycloaddition in isoxazole synthesis is the reaction between nitrile oxides and alkynes, leading to the formation of 3,5-disubstituted isoxazoles. This reaction, often referred to as the "Regitz reaction," has been extensively studied and utilized for the synthesis of various isoxazole derivatives.

Sugar-derived isoxazoles and isoxazolines represent a fascinating class of compounds with significant importance in medicinal chemistry, particularly in the development of carbohydrate-based therapeutics and glycoconjugates. These compounds are derived from the 1,3-dipolar cycloaddition reaction involving sugar-derived precursors, offering unique structural features and diverse biological activities. Here's an overview of their significance: (i) Sugar molecules serve as versatile starting materials for the synthesis of isoxazoles and isoxazolines. Various functional groups present in sugars can be selectively modified to introduce diverse chemical functionalities, allowing for the generation of structurally diverse isoxazole and isoxazoline derivatives, (ii) Isoxazoles and isoxazolines derived from sugars have shown promising biological activities, including anticancer, antimicrobial, antiviral, and anti-inflammatory properties. The presence of sugar moieties in these compounds can enhance their bioavailability, cellular uptake, and targeting specificity, making them attractive candidates for drug discovery and development, (iii) Sugar-derived isoxazoles and isoxazolines can be incorporated into glycoconjugates, which are molecules consisting of a carbohydrate moiety linked to a non-carbohydrate entity (e.g., drug, peptide, protein). Glycoconjugates play essential roles in various biological processes, including cell-cell recognition, immune response modulation, and targeted drug delivery, (iv) Sugar-derived isoxazoles and isoxazolines can serve as valuable chemical biology tools for studying carbohydrate-protein interactions, glycan biosynthesis pathways, and carbohydrate-mediated biological processes. These compounds can be functionalized with reporter groups or affinity tags to facilitate their detection and characterization in biological systems, (v) The synthesis of sugar-derived isoxazoles and isoxazolines presents several synthetic challenges due to the complexity of sugar structures and the need for regioselective and stereoselective functionalization. However, innovative synthetic strategies, such as chemoenzymatic approaches, metal-catalyzed transformations, and click chemistry reactions, have been developed to overcome these challenges and enable the efficient preparation of diverse sugar-derived heterocycles.[I,II]

Sugar Derived Isoxazole: A Brief Survey:

Carbohydrates, with their inherent chirality and diverse functional groups, serve as valuable chiral substrates in organic synthesis. Their unique structural features and stereochemical complexity make them versatile building blocks for the preparation of enantiomerically pure compounds and complex molecules. Here are some ways in which carbohydrates are utilized as chiral substrates in organic synthesis: (i) Carbohydrates are abundant natural products that serve as readily available chiral starting materials in chiral pool synthesis. Their chirality is derived from the asymmetric centers present in their structures. By exploiting the chiral information encoded in carbohydrates, chemists can access enantiomerically pure compounds without the need for elaborate chiral auxiliary or resolution steps, (ii) Carbohydrates can undergo various asymmetric transformations to introduce chiral information into target molecules. Reactions such as asymmetric aldol reactions, asymmetric hydrogenation, and asymmetric allylation using carbohydrate-derived chiral catalysts or ligands enable the stereoselective formation of new carbon-carbon and carbon-heteroatom bond, (iii) Carbohydrate-derived ligands and catalysts play essential roles in asymmetric catalysis, facilitating a wide range of transformations with high enantioselectivity. Examples include chiral phosphine ligands derived from sugars, which are employed in transition metal-catalyzed asymmetric hydrogenation and cross-coupling reactions, (iv) Carbohydrates are key components in glycosylation reactions, where they serve as both chiral donors and acceptors. By controlling the stereochemistry of glycosidic bond formation, chemists can selectively access specific anomers and glycosidic linkages, enabling the synthesis of oligosaccharides

and glycoconjugates with defined stereochemical arrangements, (v) Carbohydrates can be derivatized to serve as chiral auxiliaries in asymmetric synthesis. Functional groups such as hydroxyls and amino groups in carbohydrates can be modified with chiral groups, facilitating asymmetric induction in subsequent transformations. Carbohydrate-derived chiral auxiliaries have been employed in a variety of reactions, including asymmetric reduction, oxidation, and cycloaddition reactions, (vi) Enzymes, particularly glycosidases and glycosyltransferases, can catalyze stereoselective transformations of carbohydrates and carbohydrate-containing compounds. Enzymatic reactions offer mild conditions and high selectivity, allowing for the synthesis of complex chiral molecules under biocompatible conditions. Herein, we present a succinct yet comprehensive review elucidating the synthesis methodologies for isoxazole/isooxazoline compounds *via* 1,3-dipolar cycloaddition reactions. Noteworthy in this synthetic framework is the incorporation of carbohydrates, particularly monosaccharides, serving as chiral adjuvant. This strategic utilization underscores the crucial significance of these compounds as foundational components for the synthesis of diverse molecules, holding significant therapeutic implications.



3a, Ar: Ph, 86%, (e.r. 1:1)
3b, 2,4,6-TMP, 98%, (e.r. 1:1)
3c, 3,4,5, TMP*, 50%, (e.r. 1:1)

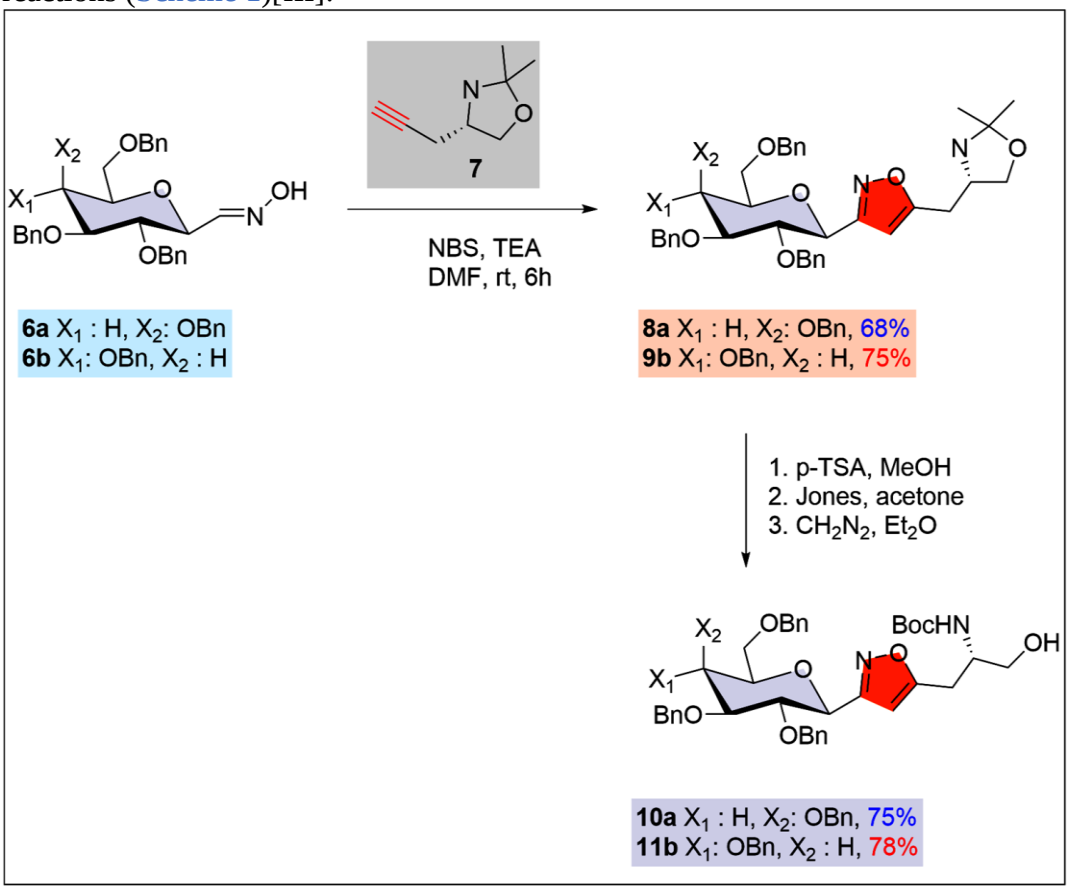
4a, Ar: Ph, 73%, (e.r. 10:1)
4b, 2,4,6-TMP, 93%, (e.r. 28:1)
4c, 3,4,5, TMP, 70%, (e.r. 11:1)

5a, Ar: Ph, 91%, (e.r. 5:1)
5b, 2,4,6-TMP, 97%, (e.r. 2.7:1)
5c, 3,4,5, TMP, 65%, (e.r. 3:1)

Scheme 1 Synthesis of Chiral Isoxazoline derived from sugar (Rollin et al. approach).

In 2002, Rollin et al. introduced a pioneering approach involving stereoselective dipolar cycloadditions of nitrile oxides to sugar-derived ethenyl ethers, serving as chiral dipolarophiles. This innovative study by Rollin and colleagues sought to elucidate the intricate stereochemical aspects inherent in the cycloaddition process. Specifically, the authors strategically employed carbohydrate enol ethers **1**, **2**, and **3**, meticulously selecting these substrates to probe the critical role of the spatial proximity between the chiral template and the reactive moiety. Furthermore, their investigation delved into the nuanced influence exerted by an epimeric distinction between the D-fructo and D-psico structural

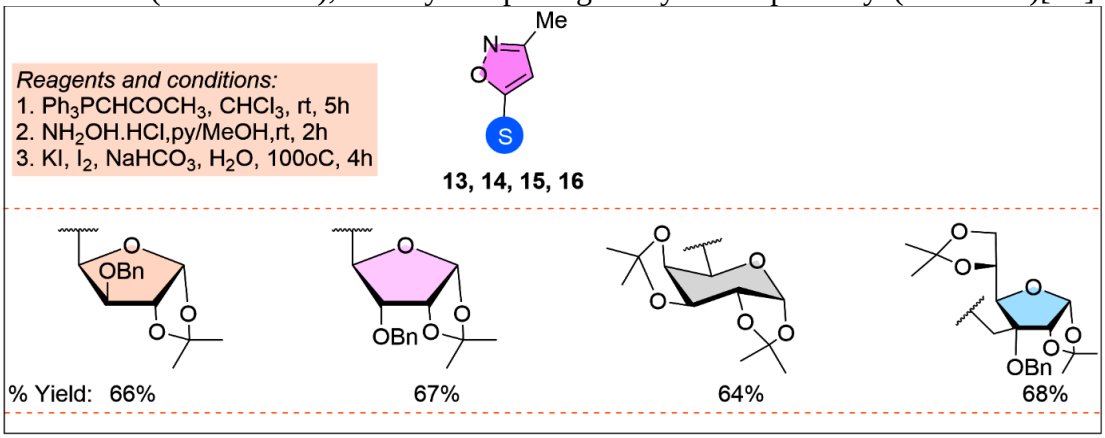
configurations. Through meticulous experimentation and analysis, Rollin et al. aimed to unravel the underlying stereochemical intricacies governing these dipolar cycloaddition reactions, thereby advancing our understanding of molecular reactivity and stereocontrol in organic synthesis. The ethenyl ethers (1-3) were synthesized efficiently from the respective carbohydrate precursors, namely, 1,2:4,5-di-O-isopropylidene-D-fructopyranose, 1,2:4,5-di-O-isopropylidene-D-psicopyranose, and 1,2:3,4-di-O-isopropylidene-D-galactopyranose, employing a concise two-step synthetic strategy. Initially, a Michael addition reaction was employed utilizing bis-phenylsulfonylethylene (BPSE) as the electrophilic component, affording the desired ethenyl ethers as intermediates. Subsequently, reductive desulfonylation was conducted, leading to the cleavage of the phenylsulfonylethyl moiety and the generation of the target ethenyl ethers (1-3) in good yields. This efficient synthetic route facilitated the rapid generation of the desired substrates, laying a solid foundation for subsequent investigations into their utility as chiral dipolarophiles in stereoselective dipolar cycloaddition reactions (Scheme 1)[III].



Scheme 2 Synthesis of isoxazole C-glycoside and a-amino acid as a biconjugate hybrid (Dondoni et al approach).

In 2004, Dondoni et al. disclosed a notable advancement in the field of organic synthesis, detailing the 1,3-dipolar cycloadditions of C-glycosyl nitrile oxides with both alkynes and azides. This transformative methodology led to the formation of disubstituted isoxazoles and triazoles, each bearing a masked glycinyl moiety. Subsequent deprotection of these cycloadducts revealed C-glycosyl β-amino acids, wherein the two bioactive components were intricately linked through rigid five-membered heterocycles. Notably, optimized synthetic routes to these compounds involved the utilization of unmasked but protected alkyne- and azide-containing amino acids as the complementary partners in the 1,3-dipolar cycloaddition reactions. This innovative approach not only enabled the efficient synthesis of biologically

relevant compounds but also provided a versatile platform for the rational design and synthesis of novel molecules with potential therapeutic applications. Building upon previous expertise in nitrile oxide generation from C-glycosyl aldoximes, the authors initiated the synthesis by subjecting a dimethylformamide (DMF) solution containing C-galactosyl oxime **6a-b** and alkyne **7a** (in a ratio of 10.0 equivalents) to N-bromosuccinimide (NBS). Subsequent dropwise addition of triethylamine (Et_3N) facilitated the reaction. Purification of the reaction mixture via chromatography yielded the desired 3,5-disubstituted isoxazole cycloadducts, denoted as **8a** and **9a**, as the exclusive regioisomers. The isolated yields were 68% to 75% respectively, demonstrating the efficiency and selectivity of the synthetic protocol. Following the successful synthesis of the 3,5-disubstituted isoxazole cycloadducts, denoted as xxa-b, the authors proceeded to obtain the corresponding α-amino acids. This transformation was accomplished through a two-step process. Firstly, the acetonide protection groups were cleaved, rendering the necessary functional groups accessible for subsequent reactions. Subsequently, an oxidation process was employed to effectuate the conversion to the desired α-amino acids. This strategic sequence of reactions, delineated in Scheme 2, enabled the final transformation of the cycloadducts into the targeted α-amino acid derivatives (**10a** and **11a**), thereby completing the synthetic pathway. (Scheme 2)[IV].



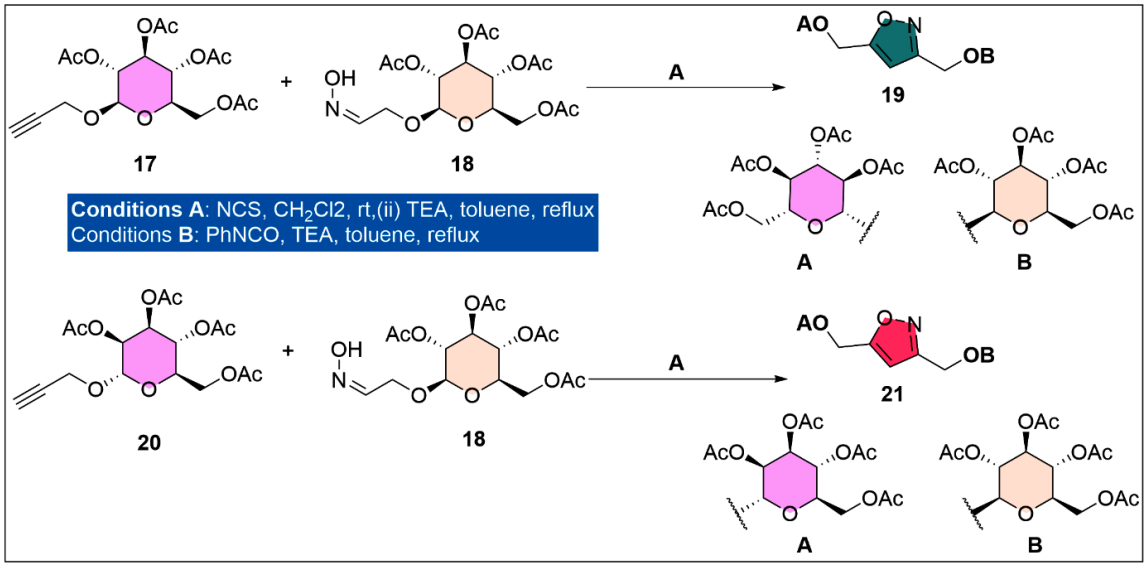
Scheme 3 Synthesis of novel isoxazole derivative linked to sugar residues (Ismael et al approach).

In 2004, the Ismael group embarked on the synthesis of novel isoxazole derivatives conjugated to sugar moieties, presenting an intriguing class of compounds reminiscent of pseudo-C-nucleosides and homopseudo-C nucleosides. The synthetic route to these isoxazoles featuring sugar moieties commenced with the preparation of formylfuranosidic derivatives. These key intermediates were synthesized through a series of synthetic steps starting from D-glucose, D-allose, and D-galactose.

The subsequent generation of isoxazole derivatives (**13-16**) involved the reaction of corresponding □□□-unsaturated oximes with a combination of potassium iodide, iodine, and sodium hydrogen carbonate at 100 ºC for 4 hours. The intramolecular oxidative cyclization of the resulting intermediates culminated in the formation of the desired isoxazoles derivatives (**13-16**) in satisfactory yields ranging from 66% to 68%. This innovative synthetic strategy enabled the efficient synthesis of isoxazole derivatives intricately linked to sugar moieties, thereby expanding the repertoire of pseudo-C-nucleosides and homopseudo-C nucleosides and offering potential avenues for diverse applications in medicinal chemistry and chemical biology (Scheme 3)[V].

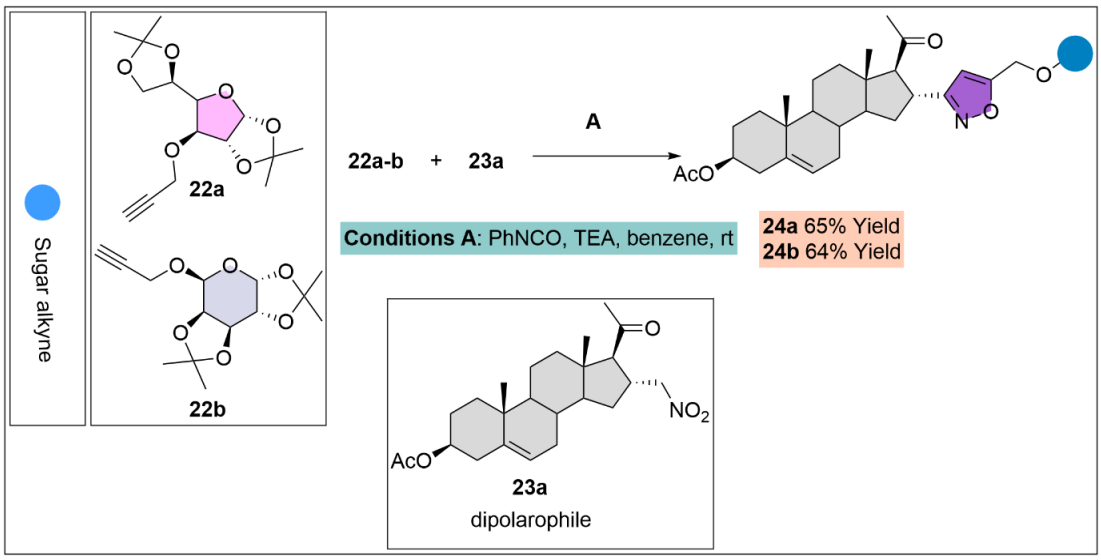
González et al. (2005) presented a sophisticated methodology for the efficient synthesis of multivalent neoglycoconjugates of isoxazole through 1,3-dipolar cycloaddition of nitrile oxides and alkynes, both derived from sugar derivatives. This approach stands out for its

elegance and expediency. The nitrile oxides are generated in situ in the presence of alkynyl derivatives, enabling the synthesis of homo- and hetero-multivalent systems containing O- and C-linked glycosides, along with isoxazole bridges. Of particular interest, the authors evaluated the Concanavalin A binding affinities of select neoglycoconjugates bearing mannose residues using the enzyme-linked lectin assay (ELLA). This analysis provided insights into the potential biological relevance of these synthesized compounds. Notably, González et al. strategically opted for D-glucose and D-mannose as counterpart sugars for the preparation of easily accessible mono nitrile oxide and mono alkynyl derivatives. This selection reflects a thoughtful approach to streamline the synthetic process while maintaining versatility in the design of glycoconjugates. urthermore, it is worth noting that these compounds exhibit a significant multivalent effect, as inferred from the comparison of their IC50 values. This observation underscores the potential utility of these neoglycoconjugates in various biological applications, where the multivalent presentation of ligands can lead to enhanced binding interactions and biological activity. The 1,3-cycloaddition of nitrile oxide and alkynes emerges as a robust methodology for the construction of synthetic multivalent carbohydrates, facilitating the assembly of these compounds from complementary functionalized building blocks. This approach has enabled the synthesis of a diverse array of divalent and multivalent



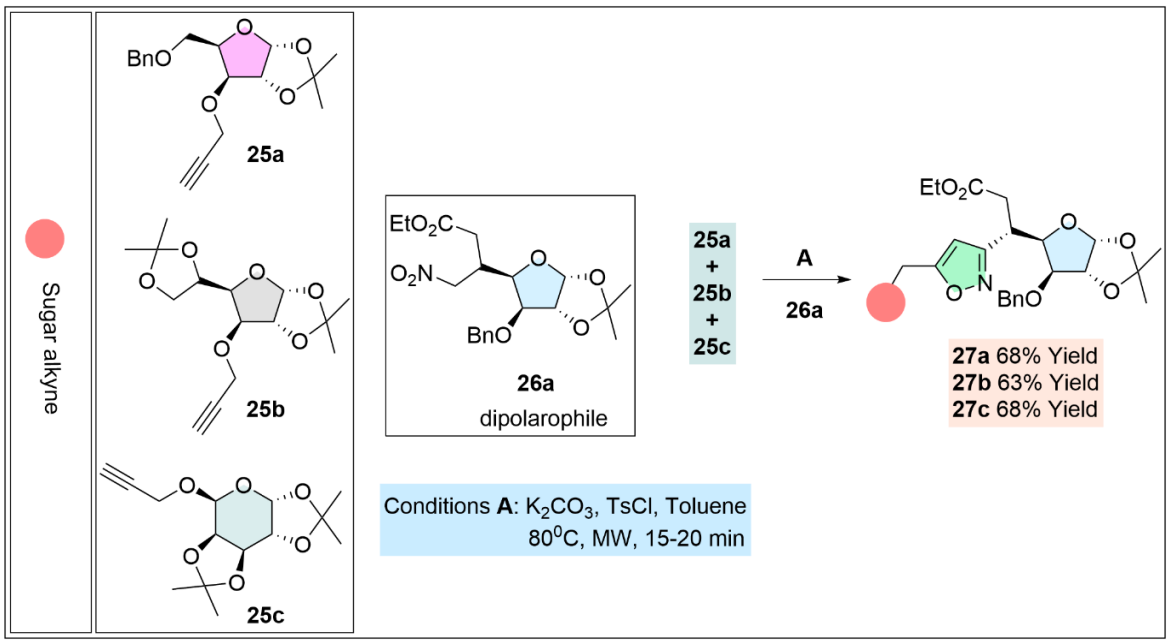
Scheme 4 Synthesis multivalent neoglycoconjugates by 1,3 dipolar cycloaddition of nitrile oxides and alkynes and evaluation of their lectin-binding affinities (González et al. approach).

Homo- and hetero-neoglycoconjugates containing both O- and C-linked glycosides (**19** and **21**). The application of this methodology has yielded significant insights into the structure-activity relationships of these compounds. Specifically, the binding affinities of select mannose-containing neoglycoconjugates with Con A were evaluated, leading to the formulation of noteworthy conclusions regarding the influence of structural variations on inhibitory properties. This evaluation highlights the potential of these synthesized compounds for further investigation and application in various biomedical contexts (Scheme 4)[VI].



Scheme 5 An expedient synthesis isoxazole-linked steroidal glycoconjugates via 1,3-dipolar cycloaddition (Trevedi et al. approach).

In 2008, Trevedi et al. introduced a highly potent methodology for accessing biologically relevant isoxazole-linked steroidal glycoconjugates through 1,3-dipolar cycloaddition reactions. This innovative approach involves the utilization of an in situ generated steroidal nitrile oxide, which subsequently undergoes coupling with appropriate propargyl ethers derived from sugars. The significance of this methodology lies in its provision of a novel vector in the form of an easily accessible nitrile oxide. This versatile intermediate exhibit the ability to couple with a wide range of biomolecules, thereby opening up a new avenue for the construction of biologically significant steroidal conjugates of isoxazoles. By offering a streamlined and efficient route to these complex conjugates. The reported approach not only expands the toolbox of synthetic chemists but also holds promise for the development of novel therapeutics and biochemical probes targeting various biological pathways. In this method, nitroalkane (23a) underwent treatment with propargyl ethers (22a-b) in the presence of phenyl isocyanate (PhNCO) and triethylamine under Mukaiyama's conditions, carried out in dry benzene at room temperature. Remarkably, this one-pot reaction demonstrated complete regioselectivity, yielding 3,5-disubstituted isoxazoles (24a-b) as the exclusive products. This efficient and selective transformation highlights the power of this synthetic approach in providing straightforward access to structurally diverse isoxazole derivatives, which hold significant potential for various applications in medicinal chemistry and chemical biology (Scheme 5)[VII].

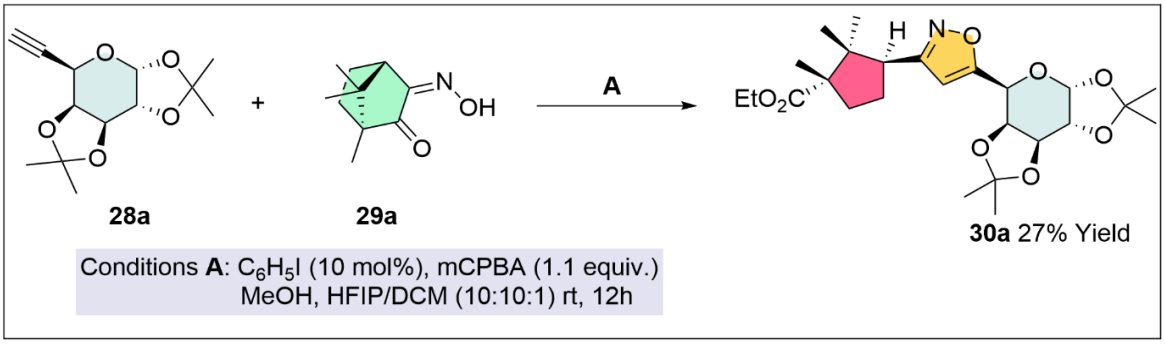


Scheme 6 A regioselective expedient synthesis of novel isoxazole linked glycoconjugates (Tiwari et al.) approach.

In 2015, Tiwari et al. introduced a concise and efficient protocol for the regioselective synthesis of novel 3,5-disubstituted isoxazole-linked glycoconjugates (27a-c). This groundbreaking approach relied on a 1,3-dipolar cycloaddition reaction between an in situ generated glycosyl-β-nitrile oxide, derived from glycosyl-β-nitromethane ester (26a), and various terminal alkynes bearing sugar residues (25a-c). Notably, the reaction proceeded with high regioselectivity, ensuring the exclusive formation of the desired products. A pivotal aspect of this work was the elucidation of the formation of the nitrile oxide intermediate during the reaction course. Utilizing Density Functional Theory (DFT) calculations, the authors obtained the optimized structure of the glycosyl-β-nitrile oxide ester, providing crucial insights into the mechanistic underpinnings of this transformation. This one-pot methodology not only represents a significant advancement in synthetic chemistry but also introduces a novel variant in click chemistry utilizing D-glucose-derived nitrile oxide. By offering a streamlined route to isoxazole-linked glycoconjugates, this approach opens up new avenues for the construction of carbohydrate-based scaffolds with multifaceted biological profiles. Such compounds hold immense promise for applications in medicinal chemistry, chemical biology, and drug discovery, contributing to the ongoing exploration of carbohydrate-based therapeutics and molecular probes (Scheme 6)[VIII].

In 2018, Kaliappan et al. introduced an innovative and efficient multicomponent reaction for the synthesis of stereo-enriched cyclopentyl-isoxazoles. This method utilized camphor-derived α-oxime, alkynes, and methanol (MeOH) as starting materials. Central to their approach was a series of cascade transformations facilitated by the in situ generation of catalyst I(III). This catalyst played a pivotal role in catalyzing several key steps, including the addition of MeOH into a sterically hindered ketone, oxime oxidation, and α-hydroxyiminium ion rearrangement. These transformations collectively generated the nitrile oxide intermediate in situ, which subsequently participated in a [3+2]-cycloaddition reaction with alkynes, ultimately yielding regioselective products. Notably, the reaction exhibited high selectivity towards the syn-oxime configuration, enhancing the stereochemical control of the final products. Building upon this multicomponent approach, Kaliappan et al. extended their methodology to the synthesis of a novel glycoconjugate, camphoric ester-isoxazole C-

galactoside (30a). This expansion underscores the versatility and applicability of their synthetic strategy, offering a streamlined route to diverse and stereochemically enriched compounds with potential applications in medicinal chemistry and chemical biology (Scheme 7)[IX].



Scheme 7 Multicomponent approach to Stereoenriched glyconjugate derived from sugar (Kaliappan et al approach).

Outlook and Future Prospect:

The outlook and future prospects of 1,3-dipolar cycloaddition in the synthesis of isoxazole glycoconjugates represent a promising avenue with substantial implications for various fields, including medicinal chemistry, chemical biology, and materials science. Here's a detailed exploration of the potential directions for further research and development in this area: (i) Continued efforts in optimizing reaction conditions, including catalyst design, solvent selection, and temperature control, can lead to enhanced efficiency, selectivity, and scalability of the 1,3-dipolar cycloaddition process. Fine-tuning these parameters will contribute to the broader utility of this synthetic strategy in the synthesis of diverse isoxazole glycoconjugates, (ii) Exploration of novel substrates, such as different sugar derivatives, alkynes, and nitrile oxides, can broaden the scope of accessible isoxazole glycoconjugates. Investigating the compatibility of various functional groups and stereochemical motifs will enable the synthesis of structurally diverse and biologically relevant compounds, (iii) The design and implementation of chemo- and stereoselective reactions within the framework of 1,3-dipolar cycloaddition will facilitate the controlled synthesis of specific regioisomers and stereoisomers of isoxazole glycoconjugates. Strategies involving catalyst-controlled or substrate-controlled transformations can provide access to complex molecular architectures with defined stereochemical features (iv) Further elucidation of the reaction mechanism and intermediates involved in 1,3-dipolar cycloaddition reactions can guide rational catalyst design and reaction optimization. Computational modeling techniques, such as Density Functional Theory (DFT) calculations, can offer valuable insights into reaction kinetics, transition states, and substrate interactions, aiding in the development of predictive models for reaction outcomes, (v) Application in Drug Discovery and Chemical Biology: Leveraging the unique structural and functional properties of isoxazole glycoconjugates, particularly their potential as carbohydrate-based therapeutics and molecular probes, holds promise for applications in drug discovery and chemical biology. Screening libraries of isoxazole glycoconjugates for biological activity against relevant targets, such as lectins, enzymes, or receptors, can lead to the identification of lead compounds with therapeutic potential (vi) The introduction of diverse functional groups onto isoxazole glycoconjugates can impart additional biological activities, improve pharmacokinetic properties, or enable conjugation to targeting moieties or biomaterials. Strategies for post-synthetic modification and diversification of isoxazole glycoconjugates will enhance their utility in various applications,

including drug delivery, imaging, and diagnostics, (vi) Scale-Up and Industrial Translation: Addressing challenges related to scalability, reproducibility, and cost-effectiveness is crucial for the industrial translation of 1,3-dipolar cycloaddition-based methodologies for the synthesis of isoxazole glycoconjugates. Process optimization, green chemistry principles, and continuous-flow technologies can facilitate scale-up while minimizing environmental impact and resource utilization. In conclusion, the continued exploration and advancement of 1,3-dipolar cycloaddition in the synthesis of isoxazole glycoconjugates offer exciting opportunities for innovation and discovery across interdisciplinary fields. By addressing key challenges and leveraging emerging technologies, researchers can harness the full potential of this synthetic strategy to access novel compounds with diverse biological activities and therapeutic applications.

Acknowledgement:
AKS expresses sincere gratitude for the invaluable support received through a grant from the Research and Development Higher Education, Lucknow, as referenced in Letter No. 89/2022/1585/70-4-2022/001-4-32-2022 of the State Government. This support has been instrumental in facilitating the research endeavors and contributions outlined in this work.

Conflict of Interest:
The author(s) declare(s) that there is a conflict of interest associated with this work.

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Received on May 14, 2024.