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Progress in the Chemistry of C-Glycosylation in Carbohydrates

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Abstract

Glycosylation is an intricate biochemical process where a glycosyl donor and a glycosyl acceptor are combined to form a glycoside. This process involves the creation of new stereogenic centers at the anomeric site of the glycosyl donor, leading to the formation of a diverse array of products. By establishing glycosidic linkages, the synthesis of complex polysaccharides becomes possible, opening doors to the creation of analogues for further exploration of their biological importance. The implications of these synthesized compounds extend to the realms of disease and various biological processes, making them key subjects for research and analysis. Within the realm of C-Glycosides, a vast spectrum of variations exists, each displaying a multitude of biologically relevant behaviors in nature. Recent advancements in the field of C-Glycosides chemistry have propelled significant developments, representing an exciting area of exploration and innovation. As we delve deeper into the complexities of C-Glycosides, the opportunities for discovering new insights into their functions and potential applications expand, indicating a promising future for research in this domain. This mini-review aims to highlight the advancements in the chemistry of C-Glycosylation, showcasing the evolution of techniques and methodologies that have driven the field forward. By examining the progress made in understanding the intricacies of C-Glycosides, we can gain valuable knowledge that may have far-reaching implications in various scientific disciplines. Through continued exploration and research in this area, the true potential of C-Glycosides can be fully unraveled, providing insights that could revolutionize our understanding of biochemical processes and their applications in real-world scenarios.

Keywords: Glycosylation, polysaccharides, c-glycosides, glycosidic bond formation, stereoselective synthesis, carbohydrate chemistry

INTRODUCTION

Carbohydrates, like glycogen and starch, play a pivotal role as the primary energy source for living organisms, serving as the main pathway for energy storage within the body. In addition to this fundamental function, carbohydrates also exert a profound influence on the regulation of various biological processes due to their structural and energy-related significance [1]. Their polar nature leads to their prevalence in the form of glycol-conjugates, where sugar units are intricately linked with other biopolymers such as proteins, lipids, and DNA, primarily located on the external surface of cells. This positioning is crucial as it directly impacts the control of both normal physiological functions and various pathological events. The abundance of carbohydrates in nature is evident

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through rich sources like sugar, starch, and fiber, prominently found in a wide array of fruits, vegetables, and dairy products [2, 3]. It is worth noting that carbohydrates constitute one of the three essential macronutrients, alongside fats and proteins, that are fundamentally vital for the proper functioning and maintenance of the human biological system. Particularly noteworthy is their role in providing fuel and energy to critical components such as the central nervous system and the musculature of the body, allowing these essential systems to function optimally. Along with that, carbohydrates are not only known to alter mood and affect memory power but also play a crucial role in various physiological processes. Glycosylation, a fundamental biochemical reaction, involves the attachment of a carbohydrate, known as a glycosyl donor, to a hydroxyl or other functional group of another molecule, referred to as a glycosyl acceptor [12, 13]. The resulting glycosidic linkages are essential bonds found in a diverse range of biomolecules, including oligosaccharides and glycoconjugates. These linkages connect sugar units or other molecules through a stable C-C bond, contributing to their wide application across different scientific disciplines. When comparing C-Glycosides to their O-congeners, it is observed that C-Glycosides exhibit significantly enhanced stability against both acidic and enzymatic hydrolyses due to the unique carbon atom linkage between the carbohydrate unit and the acceptor. This distinction from O-Glycosides, which are linked via oxygen atoms, results in C-Glycosides having a longer half-life during enzymatic and chemical breakdown processes. This enhanced stability is attributed to the robust nature of the C–C bond, which outperforms the C–O linkage in resisting hydrolytic degradation. A groundbreaking discovery in 1994 identified the first naturally occurring C-glycosyl amino acid in proteins, namely C-mannosyltryptophan, marking a significant milestone in understanding unique glycosylation patterns in biomolecules. This finding not only sheds light on the intricate interplay between carbohydrates and proteins but also highlights the potential implications of C-Glycosides in the realm of biological processes and structural biology research. The discovery of -C-mannosyltryptophan opens up new avenues for exploring the significance of C-Glycosides and their role in shaping the complexity of biological systems as shown in Figure 1. Numerus naturally occurring substances, such as plants, bacteria, and fungi, harbor a wide array of biologically active molecules possessing therapeutic qualities crucial for human health and well-being. This extensive array of bioactive compounds, ranging from secondary metabolites to specialized metabolites, owes much of its diverse chemical structures and functions to the intricate process of C-glycosylation. Through C-glycosylation, not only are pharmaceutical medications, but also various natural products utilized in traditional and modern medicine, produced in abundance. By harnessing the power of C-glycosylation, scientists and researchers are able to synthesize a broad spectrum of compounds with significant medicinal value. These compounds include essential biomolecules such as antibodies, vital for combating infections and diseases, as well as potent drugs like anticancer agents, antidiabetic medications, and anti-inflammatory remedies, crucial for treating various health conditions and improving the quality of life for millions of individuals worldwide. In comparison to the well-known O-Glycosides and N-Glycosides, the exploration and utilization of C-Glycosides in natural product and medicinal chemistry came to the forefront at a later stage, unveiling a new realm of chemical diversity and biological activities for researchers to explore and exploit [16]. This delay in recognition did not undermine the importance and potential of C-Glycosides, as their discovery has significantly broadened the scope of drug discovery and natural product chemistry, paving the way for novel therapeutic interventions and advanced medicinal breakthroughs. The fascinating world of C-glycoside products encompasses a wide range of natural compounds that have captivated the interest of scientists and pharmaceutical companies alike [14]. From rare plant extracts rich in bioactive C-glycosides, offering potential remedies for various ailments, to unique microbial metabolites displaying promising medicinal properties, the diversity and complexity of these natural products continue to inspire innovative research and drug development efforts around the globe. Some noteworthy examples of natural C-glycoside products include [7]. Overall, the remarkable impact of C-glycosylation on drug development and natural product chemistry cannot be overstated, as it represents a cornerstone in the synthesis and discovery of bioactive molecules with immense therapeutic potential, shaping the landscape of modern pharmacology and healthcare practices for the better [15]. The list below includes a few natural C-glycoside products.

PROGRESS IN THE CHEMICAL METHODS FOR THE SYNTHESIS OF C-GLYCOSIDES

In the field of C-glycoside synthesis, a significant number of techniques rely on the employment of donor precursors that serve as fundamental components of carbohydrates, thereby facilitating the direct formation of glycosidic C-C bonds. This approach, as elucidated in You Yang's comprehensive review [18], involves the utilization of glycosyl donors which can undergo C-glycosylation via multiple pathways. These pathways may include reactions with electrophilic/cationic species, anionic species, radical species, ring closure mechanisms, and interactions with transition metal complexes, all of which are depicted in Figure 2. The mini-review we present encompasses an in-depth discussion of the various chemical processes instrumental in the synthesis of C-Glycosides, shedding light on the latest advancements and breakthroughs in this domain, as illustrated in Figure 3. Through this overview, we aim to provide a comprehensive understanding of the diverse methodologies and strategies employed in the synthesis of these vital compounds, highlighting the ongoing developments and innovations that continue to drive progress in this area of organic chemistry.

DIFFERENT SYNTHETIC APPROACH OF C-GLYCOSYLATION

Nucleophilic attack on the anomeric carbon's electrophilic core is the most popular technique for forming carbon-carbon bonds at this location. Many other glycosyl halides, imidates, glycals, lactones, thioglycosides, and O-protected glycosides including p-nitrobenzoates have also been used as electrophilic sugars. Aluminates, Grignard reagents, organolithium, cuprates, silyl enol ethers, alkenes, allysilanes, allylstannanes, and homoenolates are examples of organomettalic carbon nucleophiles that have been employed. The literature from 2001 to 2013 is surveyed in this treatment. The following are some earlier C-Glycosylation reports. Maddaford et al. reported in 2001 that a Carbon-Ferrier type product was produced by the anti-elimination of $Pd(OAc)_2$ and the syn addition of a sigma-aryl-Pd complex to the glycal double bond. This technique offers a handy and useful way to synthesize C-aryl glycosides stereselectively.[13]Yenjai et al. reported in 2003 that depending on the trimethylsilyl and triisopropylsilyl groups employed, the propargylic and acetylenic silyl groups on propyne govern the C-Glycosidation products [8]. In 2008, Stefani *et al.* reported a mild and stereoselective method for C-glycosylation of D-glucal with different alkynyltrifluoroborates to provide acetylene glycoside using $BF_3.OEt_2$ [17]. Lewis acid has been used in conjunction with a palladium catalyst to create C-glycosides. A moderate palladium catalyzed C-glyosylation of easily accessible glycal derivatives was developed by Zeng et al. in 2013 [20]. Das et al. demonstrated a mild decarboxylative C-glycosylation of glycal derivatives catalyzed by palladium as shown in Figure 4. To produce the product in a high yield, this transformation entails a tandem sequence of rearrangement and decarboxylation.

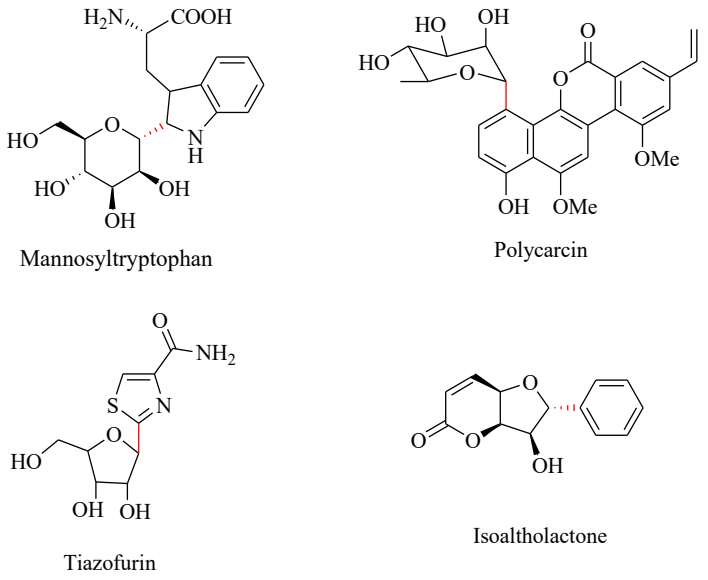

Figure 1. Natural products of C-aryl glycosides.

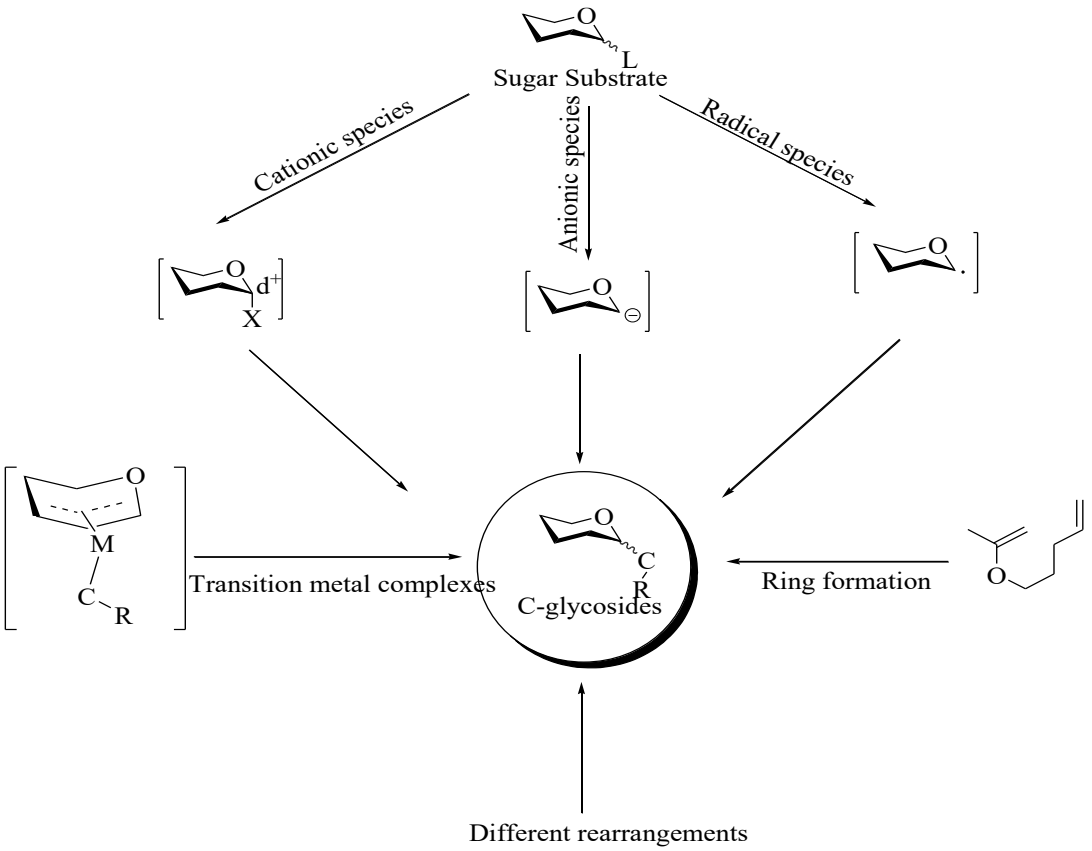

Figure 2. Major chemical method for the synthesis of C-Glycosides.

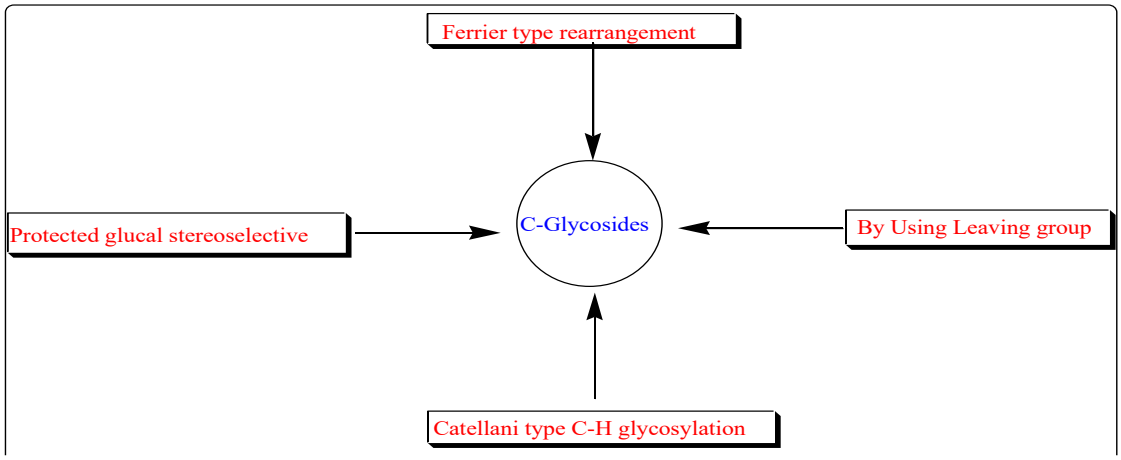

Figure 3. Progress in the chemistry of C-glycosides. Firstly, it was synthesized by Ferrier type of rearrangement followed by attaching leaving group at anomeric position of donors, catellani type of C-H glycosylation and reagent controlled stereoselective with protected glucal.

These are a few new C-Glycosylation reports that were released in 2020. C-Glycosides have been produced by a process catalyzed by copper and palladium. Using $Cu(OTf)_2$ as an activator, Ye et al. [19] have developed the C-glycosylation reaction of picolinates with aryltrimethylsilane or silyl enol ethers. Ding et al. [4] used Pd-norbornene cooperative catalysis, the first ortho C–H glycosylation reaction of aryl iodides to produce C–aryl glycosides and these reactions are easily operated, highly discriminate, and widely applicable as shown in Figure 5. Lv et al. [10] showed that a stereoselective Catellani-type C-H glycosylation process can give quick access to highly substituted a-C-(hetero) aryl glycosides [11].

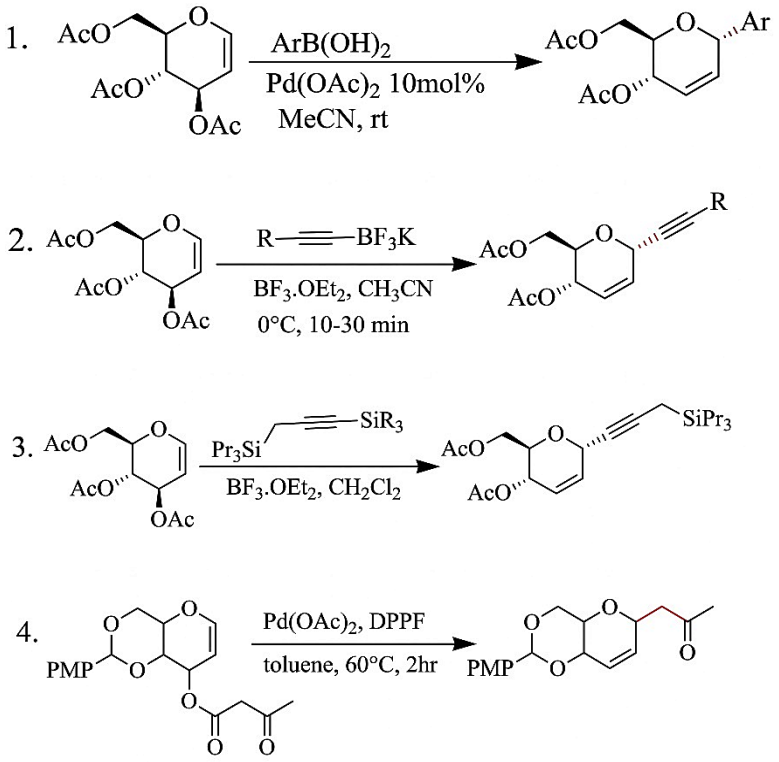

Figure 4. C-glycosylation of glycal derivative.

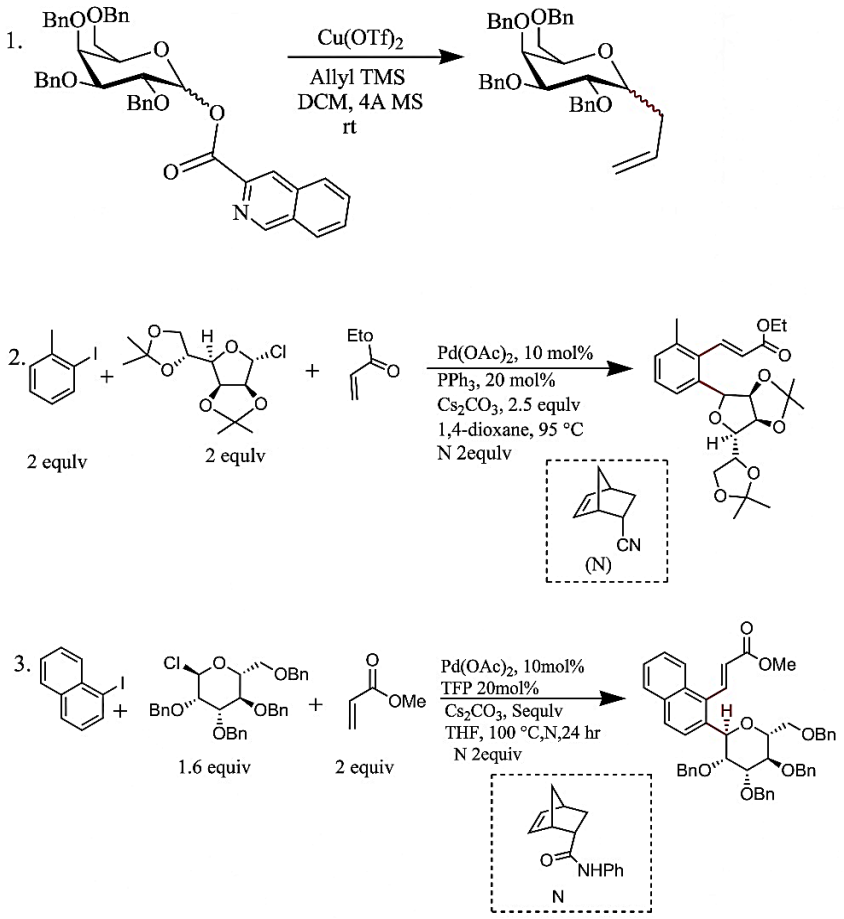

Figure 5. Substituted C- glycosylation.

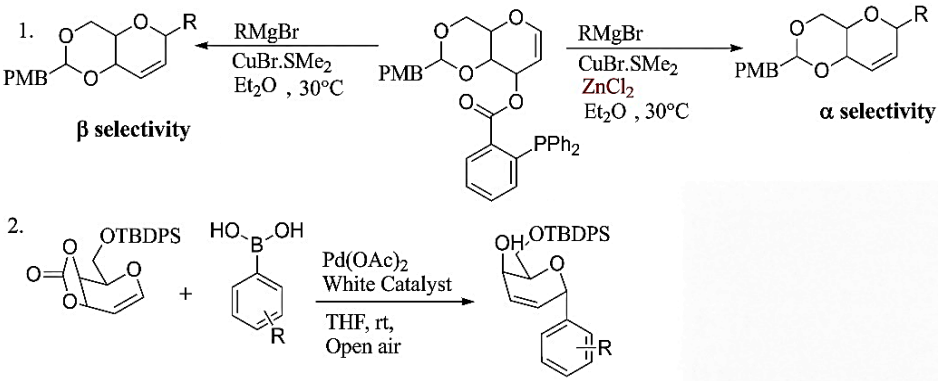

Figure 6. C- glycosylation selectivity

These are the few C-glycosides which are obtained with protected gylcal donors in 2020. Han et al. discussed reagent controlled C-glycoside synthesis with o-DPPB directing group with a good yield and broad application [6]. Lai et al. discussed the C-glycoside synthesis with protected glycal with boronic acid under open air and room temperature with good yield as shown in Figure 6. This reaction also showed C- glycosylation selectivity when hydroxyl and amino group attached to aryl boronic acid [9].

COCLUSION

In this insightful mini-review, we meticulously detailed the remarkable strides achieved in the field of C-glycosylation synthesis techniques, delving into two decades of research spanning from 2001 to 2020. The quest to conquer the synthesis of natural products boasting the elusive C-glycosidic linkage emerged as a pivotal challenge in the landscape of organic chemistry, particularly gaining momentum during the 1970s. An abundance of scholarly effort and scholarly endeavors has been devoted to unraveling the complexities surrounding the stereoselective synthesis of C-glycosides, a multifaceted process underpinned by a spectrum of C–C bond formations that intricately involve anomeric cations such as oxocarbenium cations, anomeric radicals, and anomeric anions. Furthermore, this scientific journey has been enriched by the amalgamation of sigmatropic rearrangement phenomena and the catalytic prowess of transition metals in ushering forth groundbreaking transformations within this specialized domain. This mini-review serves as a beacon of clarity, focusing keenly on elucidating the intricate reaction mechanisms that underpin the fascinating realm of C-glycosylation. A comprehensive discussion ensues, shedding light on pertinent C-glycosylations and the mechanisms that underlie their synthesis, thereby empowering readers with a deeper understanding of the intricate chemical ballet that unfolds during these processes. It is our earnest aspiration that this succinct yet potent exploration will serve as a catalyst for scientific minds to venture forth and engineer innovative methodologies that push the boundaries of C-glycosylation synthesis, ultimately shaping the landscape of organic chemistry with novel and creative approaches.

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