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Synthesis of *N*-Heteroaryl *C*-Glycosides and Polyhydroxylated Alkanes with Diaryl Groups from Unprotected Sugars

Yixuan Liu, Jilai Wu,* Likai Zhou, Chao Wei, and Hua Chen*

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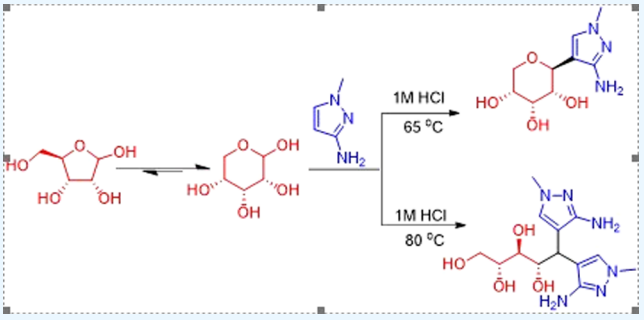
ABSTRACT: HCl-catalyzed *C*-glycosylation was described herein for the convenient preparation of *N*-heteroaryl *C*-glycosides and polyhydroxylated alkanes with diaryl groups using hetereoaryl amines and unprotected sugars as starting materials. The reaction temperature and the amounts of aryl amines and HCl had significant effects on reactions. The method provided a highly efficient and environmentally friendly route for constructing *C*-glycosides at low cost.



INTRODUCTION

N-Heteroaryl *C*-glycosides are widely used as drugs for the treatment of various cancers and bacterial or viral infections.[1]

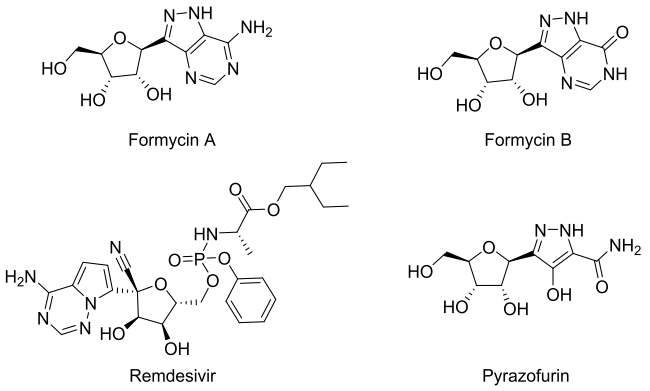


Figure 1. Representative *N*-heteroaryl *C*-glycosides with good biological activities.

Since the glycosidic bond of natural or synthetic *N*-glycosides is vulnerable in enzymatic or acid-catalyzed hydrolysis, their bioavailability is reduced.[2] However, when the *C*−*N* bond is replaced by the *C*−*C* bond, the *C*-glycoside analogues exhibit better stability in both enzymolysis and chemical hydrolysis than traditional *N*-glycosides and have special biological activities.[3] For example (Figure 1), Remdesivir,[4] the synthetic *C*-nucleoside, displays broad-spectrum antiviral activities as a potential drug for COVID-19. Pyrazofurin[5] is a pyrazole-derived *C*-nucleoside with significant antitumor activity. Formycin A[6] and B[7] are natural antibiotics.

So far, good progress has been achieved in elucidating biosynthetic pathways[8] for these *N*-heteroaryl *C*-glycosides, while they are generally obtained by a multistep synthesis method in a chemistry lab. The synthesis of *N*-heteroaryl *C*-glycosides has still been a great challenge due to the installation and removal of specific protective groups on the synthetic chemistry of carbohydrates.[9] Recently, Niu's group[10] (Scheme 1a) developed an efficient protocol for preparing *C*-nucleosides from unprotected glycosyl sulfinate, which was used as the radical precursor to generate a glycosyl radical under a highly acidic environment to react with pyridine through the Minisci reaction. Ding's group[11] (Scheme 1b) achieved the *C*−*H* glycosylation of glycosyl chlorides and *N*-Pym indole via palladium catalysis. Xia's group[12] (Scheme 1c) developed a photoredox-catalyzed radical coupling of glycosyl bromides with nonfunctionalized heteroarenes to construct *C*-nucleoside analogues. Both Toshima's group[13] and Sato's groups[14] (Scheme 1d,e) selected the unprotected sugars to directly couple with naphthol and phenol to give the corresponding *C*-glycosides catalyzed by (TMSOTf)-$AgClO_4$ or $Sc(OTf)_3$, respectively. Although direct *C*-glycosylation has been well developed,[15] the modular synthesis of *N*-heteroaryl *C*-glycosides from unprotected carbohydrates is still difficult due to the inherent reactivity of the hydroxyl groups on the sugar ring.[16]

Herein, we would like to report the HCl-catalyzed synthesis of *N*-heteroaryl *C*-glycoside **3** starting from the unprotected

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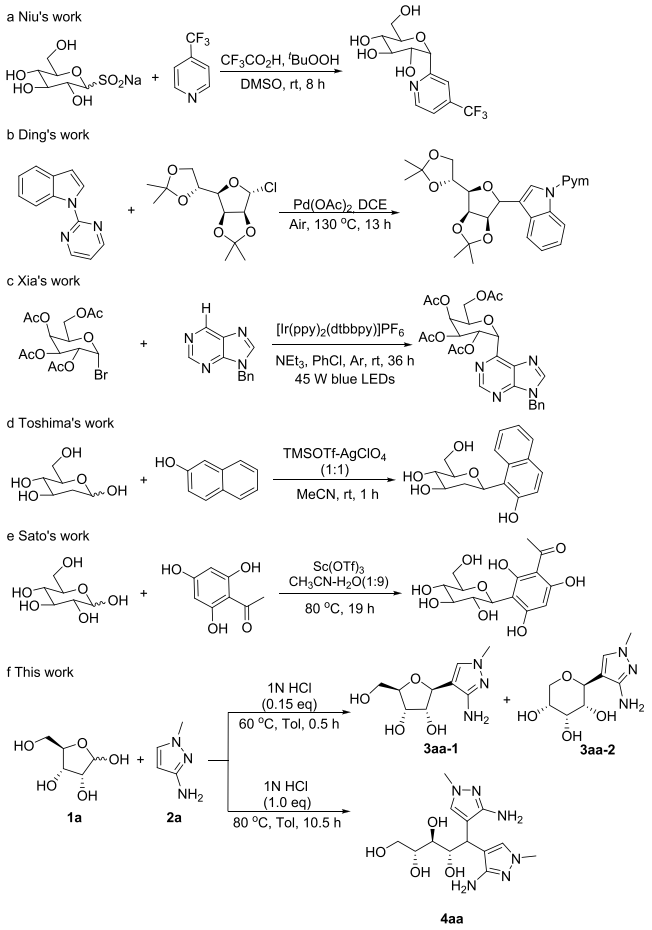
Scheme 1. Different Methods to Synthesize Aryl *C*-Glycosides

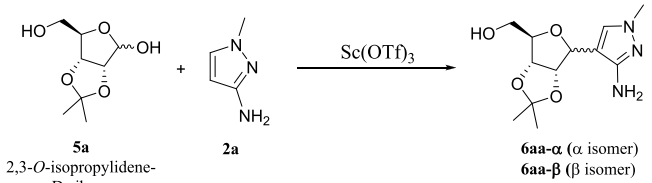


sugar under metal-free conditions (Scheme 1f). In addition, a series of polyhydroxylated alkanes with diaryl groups **4** were also achieved by regulating the reaction temperature and the amounts of aryl amines and HCl.

RESULTS AND DISCUSSION

In the study on the synthesis of fused multicyclic iminosugars,[17] our group accidentally found that 2,3-*O*-isopropylidene-D-ribose(**5a**) reacted with *N*-methyl 3-aminopyrazole (**2a**) to afford a pair of *N*-heteroaryl *C*-glycosides (**6aa-*α*** and **6aa-*β***) with a diastereoisomer ratio of 1:1.5 (*α*:*β*) using $Sc(OTf)_3$ as a catalyst in the mixed solvents of toluene and methanol (Scheme 2). The structure of **6aa-*α*** was determined by its NMR spectra and X-ray crystallographic data (CCDC No: 2349237).

Scheme 2. Synthesis of 6aa[a]



[a]Reagents and conditions: The solution of 2,3-*O*-isopropylidene-D-ribose **5a** (0.5 mmol, 1.0 equiv), *N*-methyl-3-aminopyrazole **2a** (2.0 equiv), and $Sc(OTf)_3$ (0.4 equiv) in toluene (2.5 mL)/methanol (0.5 mL) was stirred at 80 °C in a pressure tube for 3 h.

Considering the high reactivity of the aryl ring of **2a**, naked D-ribose **1a** and *N*-methyl-3-aminopyrazole **2a** were selected as model substrates for conditional optimization (Table 1). First, $Sc(OTf)_3$ and 1 N HCl aqueous solution were used as acid catalysts, and D-ribose **1a** reacted with **2a** (1.5 equiv) at 65 °C for 10.5 h until the products did not change anymore on silica gel thin-layer chromatography (entries 1−3). It could be seen that when $Sc(OTf)_3$ was used as a catalyst, almost no products were found. However, the reaction in 1 N HCl aqueous solution (absolute HCl was 0.15 equiv) could perform smoothly to afford target **3aa** of 39% accompanied by unexpected **4aa** of 21% (entry 3), which was confirmed as a polyhydroxy alkane with two aminopyrazoles by its NMR spectra (Figures S153−S155, see the Supporting Information). In fact, **1a** was consumed completely after 0.5 h, and furanoside **3aa-1** and pyranoside **3aa-2** were major products, while **4aa** was trace. As the time prolonged, **3aa-1** and **3aa-2** would be converted to **4aa** slowly. Subsequently (entries 4−6), when the reaction temperature was 60 °C, the reaction was carried out with the aid of 1 N HCl to generate the highest total isolated yields of 78% of **3aa-1** and **3aa-2** with the near equal ratio of 1:1.2 within 0.5 h, while trace **4aa** was observed (entry 5). The low amount of **2a** (1.2 equiv) would reduce the yield of **3aa** markedly (entry 7). Next, in order to improve the yield of **4aa**, the amount of **2a** was increased to 3.0 equiv in the second round of optimization. As the amount of 1 N HCl increased, the total yields of **3aa** and **4aa** improved (entries 8−11). The temperature and solvents were also optimized (entries 12−16), and the results showed that the high temperature of 80 °C and a nonpolar solvent such as toluene were beneficial for the reaction to produce **4aa** with the highest yield of 88% (entry 13). The reactions produced trace *C*-glycoside **3aa** when 1.0 equiv of HCl was used at 80 °C (entries 13−16). When 1 N HCl (0.15 equiv instead of 1.0 equiv) was used, the reaction afforded **4aa** with 39% yield and trace **3aa** at 80 °C (entry 17). When **2a** (1.5eq instead of 3.0 equiv) reacted with D-ribose under optimal conditions in entry 13, both **3aa** and **4aa** were trace (entry 18). The controlled experiments showed that enough acid and temperature were necessary for the generation of **4aa** in high yield, and the amount of **2a** should be above 2.0 equiv, while for the preparation of **3aa**, the reaction temperature and the amounts of HCl and **2a** should be reduced properly. Additionally, by carefully monitoring the reaction process, a small amount of furanoside **3aa-1** was formed first, followed by a large amount of pyranoside **3aa-2**, but there was no transformation between them. There was also no transformation between the *α*/*β* isomers of compound **3aa**.

The reactions of different natural sugars and aromatic amines were explored under optimal conditions for **3aa**, and a series of corresponding *N*-heteroaryl *C*-glycosides were obtained (Tables 2 and3). In Table 2, pentoses such as L-ribose, D-lyxose, D-arabinose, and D-xylose could react with **2a** to generate target *N*-heteroaryl *C*-glycosides **3ba−3ea** with good yields of 69%−90%, while yields of 45−74% (**3fa−3ha**) could be obtained when hexoses such as D-glucose, D-galactose, and D-mannose were used. However, the reaction time of the latter should be extended to 13 h. For two disaccharides, namely, D-maltose and D-lactose, the conditions for **4aa** were adopted to produce corresponding *C*-glycosides **3ia** and **3ja** with yields of 53 and 70%, respectively. All of the reactions

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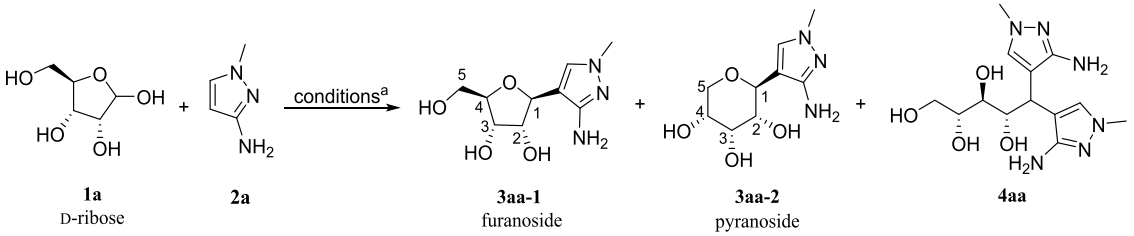
Table 1. Optimization of the Reaction Conditions for 3aa and 4aa[a]



1a D-ribose | **2a** | **3aa-1** furanoside | **3aa-2** pyranoside | **4aa**

entry	catalyst (equiv)	**2a** (equiv)	solvent (mL)	temperature (°C)	time (h)	yield of **3aa** (%)[b]	yield of **4aa** (%)[c]
1	$Sc(OTf)_3$ (0.1)	1.5	toluene (1.5)	65	10.5	N. D.[d]	N. D.
2	$Sc(OTf)_3$ (0.3)	1.5	toluene (1.5)	65	10.5	N. D.	N. D.
3	1 N HCl[e] (0.15)	1.5	toluene (1.5)	65	10.5	39	21
4	1 N HCl (0.15)	1.5	toluene (1.5)	65	0.5	61	trace
5	1 N HCl (0.15)	1.5	toluene (1.5)	60	0.5	78	trace
6	1 N HCl (0.15)	1.5	toluene (1.5)	50	0.5	67	trace
7	1 N HCl (0.15)	1.2	toluene (1.5)	65	0.5	62	trace
8	1 N HCl (0.15)	3.0	toluene (1.5)	65	10.5	trace	36
9	1 N HCl (0.4)	3.0	toluene (1.5)	65	10.5	20	53
10	1 N HCl (0.5)	3.0	toluene (1.5)	65	10.5	22	60
11	1 N HCl (1.0)	3.0	toluene (1.5)	65	10.5	31	66
12	1 N HCl (1.0)	3.0	toluene (1.5)	40	10.5	26	62
13	1 N HCl (1.0)	3.0	toluene (1.5)	80	10.5	trace	88
14	1 N HCl (1.0)	3.0	CH_3CN (1.5)	80	10.5	trace	30
15	1 N HCl (1.0)	3.0	THF (1.5)	80	10.5	trace	66
16	1 N HCl (1.0)	3.0	DCM (1.5)	80	10.5	trace	40
17	1 N HCl (0.15)	3.0	toluene (1.5)	80	10.5	trace	39
18	1 N HCl (1.0)	1.5	toluene (1.5)	80	10.5 (5.0)[f]	trace	trace

[a]Reaction conditions: D-ribose **1a** (0.5 mmol, 1.0 equiv), oil bath heating, air atmosphere. [b]Total isolated yields of **3aa-1** and **3aa-2**. [c]Isolated yield. [d]Not detected. [e]HCl aqueous solution. [f]The reactions were carried out for 5.0 and 10.5 h.

afforded pyranosides with α/β diastereoisomers as major products (**3ca**, **3ea**, and **3fa**−**3ja**), except the reactions of D/L-ribose, in which the furanoside and pyranoside were obtained (**3aa-1**/**-2** and **3ba-1**/**-2**), and in both of them, H-1 and H-2 were in trans configurations deduced from the observed large coupling constants (**3aa-1**: $J_{H\text{-}1/H\text{-}2}$ = 6.8 Hz, **3aa-2**: $J_{H\text{-}1/H\text{-}2}$ = 9.6 Hz; **3ba-1**: $J_{H\text{-}1/H\text{-}2}$ = 6.6 Hz, **3ba-2**: $J_{H\text{-}1/H\text{-}2}$ = 9.6 Hz, Table S1, see the Supporting Information). Only in the case of D-arabinose, four isomers including α/β furanosides (**3da-1-*β***: $J_{H\text{-}1/H\text{-}2}$ = 3.2 Hz and **3da-1-*α***: $J_{H\text{-}1/H\text{-}2}$ = 7.3 Hz) and α/β pyranosides (**3da-2-*β***: $J_{H\text{-}1/H\text{-}2}$ = 1.5 Hz and **3da-2-*α***: $J_{H\text{-}1/H\text{-}2}$ = 9.6 Hz) were found at the same time. The structures of furanoside or pyranoside were determined by the key crossing peaks of C-4/H-1 and C-5/H-1 in their HMBC spectra. In the HMBC spectrum of furanoside, H-1 and C-4 should have obvious crossing correlations, while in that of pyranoside, H-1 and C-5 had crossing correlations. The former was found in the 2D NMR spectra of **3aa-1**, while the latter existed in those of **3aa-2**, **3ca**, and **3ea**. The above results indicated that thermodynamic pyranosides would be major products derived from pentoses, in accordance with those reported in the literature.[9] The α/β-anomers were determined on the coupling constant of H on anomeric carbon (Table S1). In most instances, the ratios of α/β-anomers were low, but in three cases of **3h**, **3i**, and **3j**, the high ratios (above 10:1) of α/β diastereoisomers were found.

In Table 3, only two 3-aminopyrazole bases could smoothly react with **1a** to give pyranosides **3ab** and **3ac** in satisfactory yields. However, when several 5-aminopyrazole bases were used as reactants, except for **3ae**, **3af**, and **3an**, the others could efficiently react with **1a** under optimal conditions to afford the corresponding *N*-heteroaryl *C*-glycosides **3ad**−**3ap** with yields of 35−60%. It should be noted that, except for **3ad**−**3ap**, the corresponding α/β pyranosyl *N*-glycosides were also obtained with low total yields below 5%. The ^1H and ^{13}C NMR spectra of *N*-glycosides **3ag'** and **3ap'** derived from **2g** and **2p**, respectively, as examples are displayed in the Supporting Information (Figures S83−S86 and S119−S122), in which the signals of two protons on pyrazole rings appeared. By carefully monitoring the reaction process, we found that a large amount of *N*-glycosides was formed first, and then they would be transformed into the corresponding *C*-glycosides. The reactions were performed incompletely, which resulted in a small amount of *N*-glycosides remaining.

For other bases, the reactions of 2-aminopyridine, 5-aminoindole, and 5-aminoisoxazole give pyranosyl *C*-glycosides **3aq**, **3ar**, and **3as** with yields of 20−63%, respectively. The structures of **3ar-*α*** and **3ar-*β*** were determined by their 2D NMR spectra (Figures S182−S184, see the Supporting Information).

For convenient applications and modifications of aminopyrazole in such *N*-heteroaryl *C*-glycosides, the reactions of sugars with different protective groups and **2a** were also investigated (Table 4). It was found that no matter whether isopropylidene, benzyl, or acetyl protective groups were used, the reactions succeeded in yielding the expected products in high yields (61−83%). Additionally, under optimal conditions, **1a** (10 mmol) and **2a** were used as starting materials for the gram-scale reaction, and the total yields of **3aa-1** and **3aa-2** reached 65%.

A control reaction of **1a** and *N*-methylpyrazole was performed under optimal conditions for **3aa**; however, the

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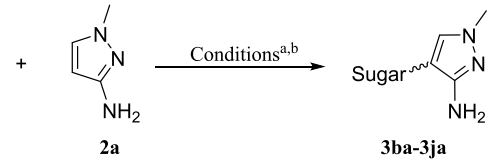
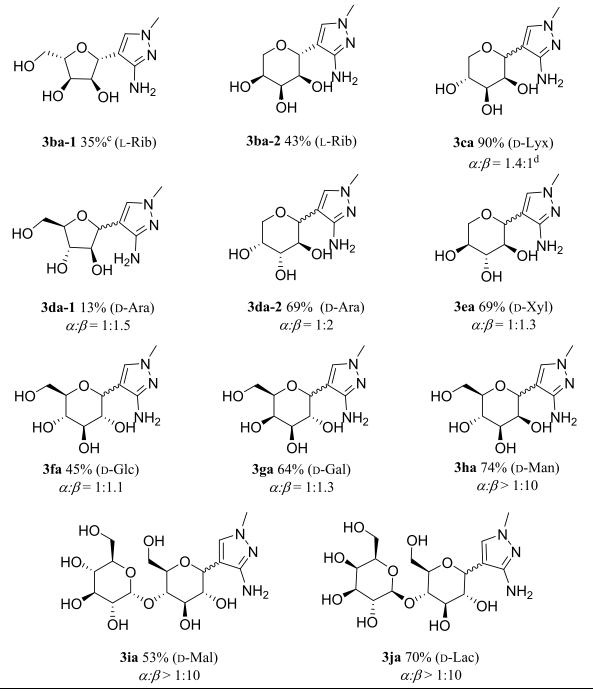
Table 2. Synthesis of *N*-Heteroaryl *C*-Nucleosides from Various Sugars and 2a

1b: L-Ribose
1c: D-Lyxose
1d: D-Arabinose
1e: D-Xylose
1f: D-Glucose
1g: D-Galactose
1h: D-Mannose
1i: D-Maltose
1j: D-Lactose

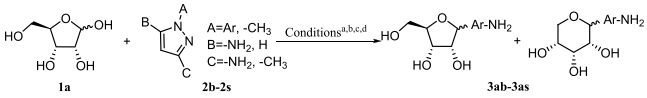


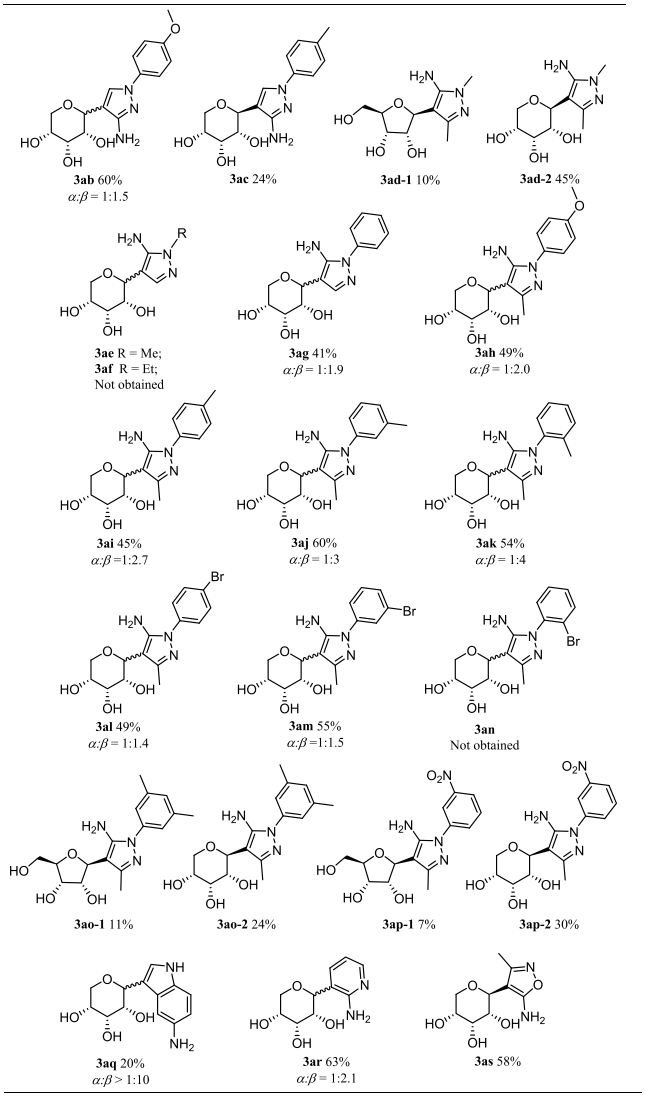
2a **3ba-3ja**



[a]Reaction conditions: The solution of sugar **1** (0.5 mmol, 1.0 equiv), **2a** (1.5 equiv), and 1 N HCl (0.15 equiv) in toluene (1.5 mL) was stirred at 60 °C in a pressure tube for 0.5 h for **3ba**−**3ea**, and 13 h for **3fa**−**3ha**. [b]For **3ia** and **3ja**, the conditions were the same as those for **4aa**. [c]Isolated yield. [d]The ratio of α/β isomers was determined by ^{1}H NMR.

Table 3. Synthesis of *N*-Heteroaryl *C*-Glycosides from 1a and Different Bases





[a]Reaction conditions: The solution of sugar **1a** (0.5 mmol, 1.0 equiv), **2** (1.5 equiv), and 1 N HCl (0.15 equiv) in toluene (1.5 mL) was stirred at 60 °C in a pressure tube for 10 min for **3ab** and **3ac** and 0.5 h for **3ad**−**3ap** and **3as**. [b]For **3aq** and **3ar**: toluene (2.0 mL), 13 h, r.t for **3aq**, 60 °C for **3ar**. [c]Isolated yield. [d]The ratio of α/β isomers was determined by ^{1}H NMR.

reaction did not occur, which suggested the important participation of neighboring NH_2. Additionally, sole *N*-glycoside **3ag'** (the mixture of **3ag'-*α*** and **3ag'-*β***) could be converted into the corresponding *C*-glycoside **3ag** with a yield of 65% under optimal conditions for **3aa** (Scheme 3). With these results in hand, a reasonable mechanism was described according to similar studies in the literature[18] (Scheme 4). First, in an acidic environment, D-ribose was activated to generate a highly reactive oxocarbenium intermediate that was then susceptible to be attacked by NH_2 to produce *N*-nucleoside **A** as the intermediate. Subsequently, a *N*−*C* Fries rearrangement occurred through ion pair **B** derived from *N*-glycoside **A** in HCl to generate *C*-glycoside **3aa-2**. Through the same process, **3aa-1** should be produced from corresponding intermediate **A'** (*N*-furanoside). Based on the analysis of the NOE spectra of **3aa-1** and **3aa-2** (Figures S174 and S178, see the Supporting Information), it was found that in this process, the configuration of the 2-position of the product remained unchanged. In compound **3aa-1**, the configuration of H-4 remained unchanged, and no cross-signal between H-4 and H-2 was found in the NOE spectrum, indicating that the configuration of H-2 did not change. In the NOE spectrum of **3aa-2**, there was a clear cross-signal peak between H-4 and H-2, which also proved that the configuration of H-2 did not change.

Bispyrazolyl derivatives have attracted much interest because they exhibit a wide range of biological activities,[19] and they are chelating and extracting reagents for different metal ions.[20] They can also be applied as ligands in metal-catalyzed reactions.[21] Many strategies for their preparation were focused on the coupling reactions of aryl aldehyde and pyrazole;[22] however, the bispyrazolyl derivatives derived from sugar aldehyde have rarely been reported. Nonetheless, the

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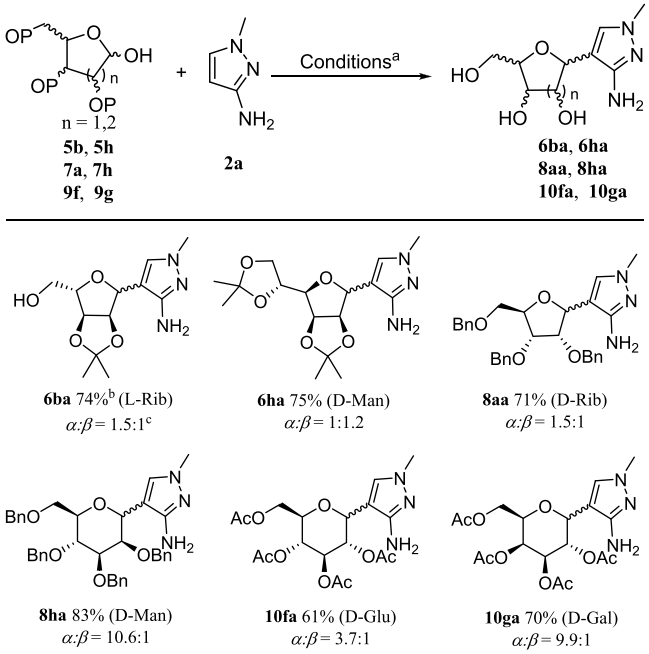
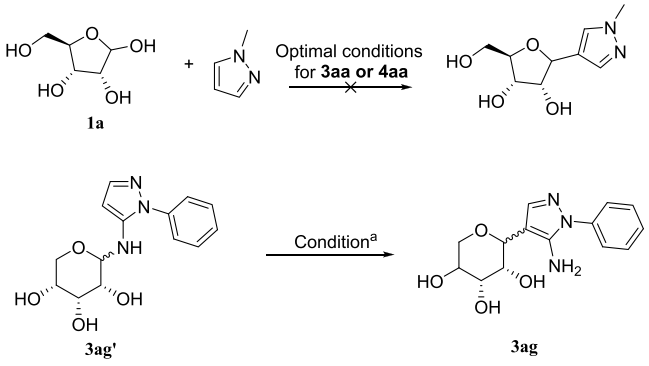
Table 4. Synthesis of *C*-Nucleosides from Protected Sugars



[a]Reaction conditions: The solution of **5** (or **7**, **9**, 0.5 mmol, 1.0 equiv) and **2a** (1.5 equiv) in toluene (2.0 mL) was stirred at 55 °C in a pressure tube for 13 h, 1 N HCl (0.15 equiv) for **6ba** and **6ha**; $Sc(OTf)_3$ (0.1 equiv) for **8aa**, **8ha** and **10fa**, **10ga**. [b]Isolated yield. [c]The ratio of α/β isomers was determined by ^1H NMR.

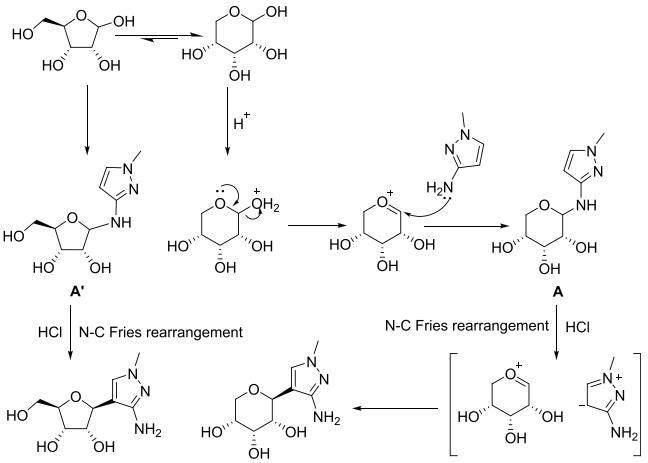
Scheme 3. Control Experiments for Mechanistic Studies[a]



[a]Reaction conditions: [a]The solution of **3ag′** (0.5 mmol, 1.0 equiv) and 1 N HCl (0.15 equiv) in toluene (1.5 mL) was stirred at 60 °C in a pressure tube for 0.5 h.

polyhydroxylated alkanes with diaryl groups, such as a natural 2,3′-bis(indolyl)methane alkaloid (colletotryptin A), offer access to new and exciting chemical scaffolds due to their significant anticancer and anticholinesterase activities.[23] Since there is great interest, the reactions of different unprotected sugars and various aminopyrazoles were investigated under the optimal conditions of **4aa**, and a series of novel corresponding polyhydroxylated alkanes with two amino bases were prepared (Table 5). The results showed that L-ribose, D-lyxose, D-xylose, D-arabinose, D-glucose, and D-galactose could be employed to react with **2a** to successfully afford target products **4ba**−**4ga** with good yields of 38−98%, while the reactions of **1a** and different 5-aminopyrazoles could be carried out efficiently to generate **4ad**−**4af**, **4ai**, and **4al** with satisfactory yields of 38−

Scheme 4. Plausible Reaction Mechanism for 3aa



97%. Other bases such as 5-aminooxazole, 2,6-diaminopyridine, and 5-aminoindole were used; however, corresponding products **4as**, **4au**, and **4av** were obtained with low yields of 13−32%. The activation of the amino group on the *N*-heteroaryl ring has a significant effect on the reaction. For example, the monoaminopyridine could not react with D-ribose (**1a**) to yield the corresponding polyhydroxy alkane, possibly due to the low reactivity of pyridine. Meanwhile, under optimal conditions, **1a** (10 mmol) and **2a** were used as starting materials for the gram-scale reaction, and the yield of **4aa** was 73%.

In order to elucidate the possible mechanism for the formation of **4aa**, a control reaction of **3aa-2** and *N*-methylpyrazole was carried out under optimal conditions for **4aa** (Scheme 5). However, the reaction could not occur. The negative result indicated that the neighboring NH_2 on pyrazole was also important for the formation of **4aa**, which suggested that a *N*−*C* Fries rearrangement possibly occurred again in the conversion from **3aa** to **4aa**. Then, a possible reaction mechanism for **4aa** is expressed in Scheme 5. First, the resonance effect originated from the lone electron pair in *N*-1 on the pyrazole ring of **3aa-2**, resulting in the sugar ring opening to generate intermediate **C** with a positive charge. Subsequently, the NH_2 group on another **2a** attacked **C** to produce *N*-substituted alkane derivative **D** (not be obtained) that might be converted into ion pair **E** quickly. Finally, a second *N*−*C* Fries rearrangement reaction afforded **4aa** from **E**.

When *m*-OCH_3- or *m*-SCH_3-substituted aniline was adopted to react with **1a** under optimal conditions, unfortunately, the reaction could not go on smoothly. However, using $Yb(OTf)_3$ as a catalyst (Table 6), 2,3-*O*-isopropylidene-D-ribose (**5a**) reacted with the substituted aniline to give polyhydroxy alkane **6aw** (or **6ax**) in low yields.

CONCLUSIONS

In summary, a series of *N*-heteroaryl *C*-glycosides and polyhydroxylated alkanes with two bases were prepared conveniently by using unprotected sugars at different temperatures and different amounts of aryl amines and HCl. Further studies on the synthesis of the valuable glucosides are ongoing in our laboratory.

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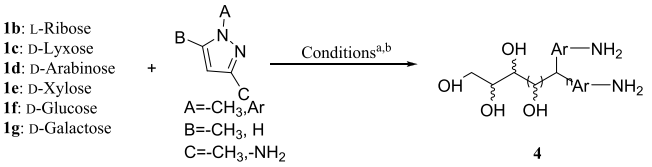
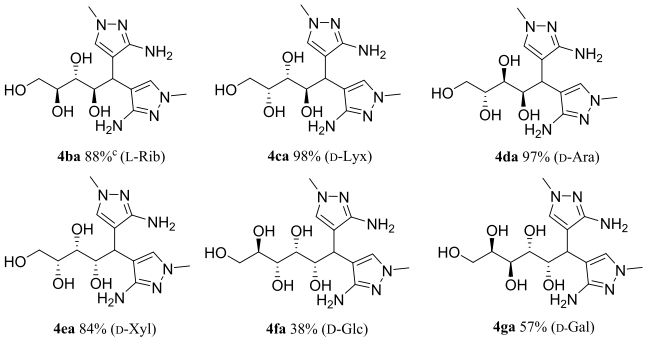
ACS Omega 2024, 9, 49618−49624

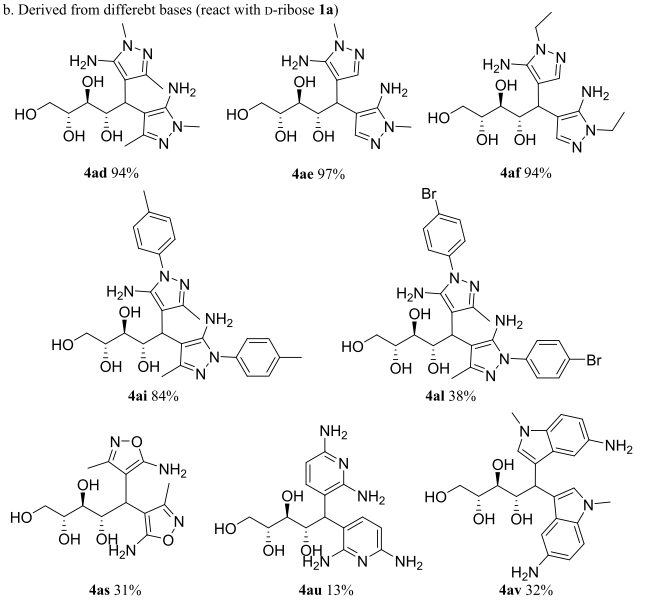
Table 5. Synthesis of Polyhydroxylated Alkanes 4 from Various Sugars and Aryl Amines



a. Derived from different sugars (react with *N*-methyl-3-aminopyrazole **2a**)



b. Derived from differebt bases (react with D-ribose **1a**)



[a]Reaction conditions: The solution of sugar **1** (0.5 mmol, 1.0 equiv), **2** (3.0 equiv), and 1 N HCl (1.0 equiv) in toluene (1.5 mL) was stirred at 80 °C in a pressure tube for 10.5 h for **4ba**−**4ga**, **4ad**−**4af**, **4ai**, **4al**, and **4as**. [b]For **4au** and **4av**: D-ribose **1a** (0.5 mmol, 1.0 equiv), **2u**−**2i** (1.5 equiv), 1 N HCl (0.2 equiv), toluene (1.5 mL), 60 °C, 13 h. [c]Isolated yield.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.4c07671.

Compound data (NMR, HR-MS, and crystallographic data) (PDF)

Accession Codes

CCDC 2349237 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: + 44 1223 336033.

Scheme 5. Plausible Reaction Mechanism for 4aa

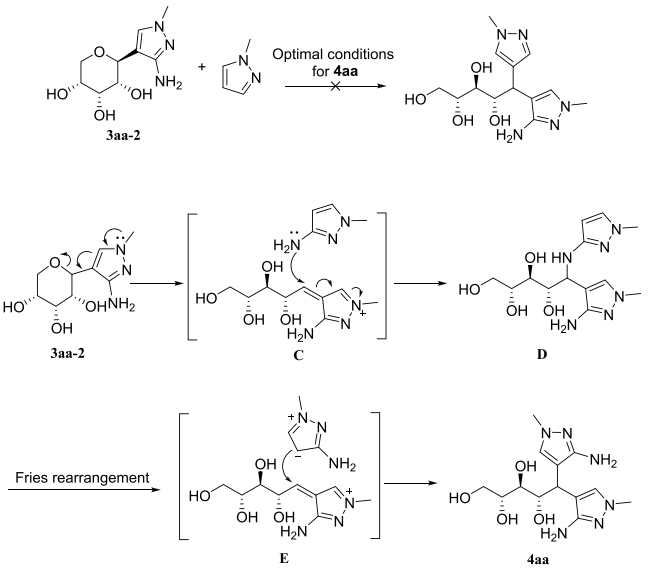
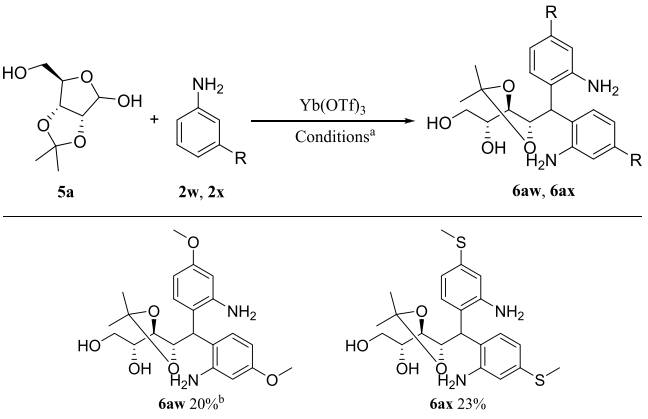


Table 6. Synthesis of 6aw and 6ax



[a]Reaction conditions: The solution of 2,3-*O*-isopropylidene-D-ribose **5a** (0.5 mmol, 1.0 equiv), **2w** or **2x** (2.0 equiv), and $Yb(OTf)_3$ (0.4 equiv) in toluene (2.5 mL)/methanol (0.5 mL) was stirred at 80 °C in a pressure tube for 3 h. [b]Isolated yield.

■ AUTHOR INFORMATION

Corresponding Authors

Hua Chen − *Key Laboratory of Chemical Biology of Hebei Province, College of Chemistry and Material Science, Hebei University, Baoding, Hebei 071002, P. R. China*; Email: huatodd@163.com

[‖]**Jilai Wu** − *Key Laboratory of Chemical Biology of Hebei Province, College of Chemistry and Material Science, Hebei University, Baoding, Hebei 071002, P. R. China; Comprehensive Experimental Center, Hebei University, Baoding, Hebei 071002, P. R. China*; orcid.org/0000-0002-8236-0709; Email: 18830269515@163.com

Authors

Yixuan Liu − *Key Laboratory of Chemical Biology of Hebei Province, College of Chemistry and Material Science, Hebei University, Baoding, Hebei 071002, P. R. China*

Likai Zhou − *Key Laboratory of Chemical Biology of Hebei Province, College of Chemistry and Material Science, Hebei University, Baoding, Hebei 071002, P. R. China; Functional*

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Polymer Materials R&D and Engineering Application Technology Innovation Center of Hebei, College of Chemical Engineering and Biotechnology, Xingtai University, Xingtai, Hebei 054001, P. R. China; orcid.org/0009-0003-4904-6579

Chao Wei − *Key Laboratory of Chemical Biology of Hebei Province, College of Chemistry and Material Science, Hebei University, Baoding, Hebei 071002, P. R. China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.4c07671

Notes

The authors declare no competing financial interest.

[‖]Co-first author.

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■ NOTE ADDED AFTER ASAP PUBLICATION

Due to a production error, Tables 2-6 were incomplete in the version that was published November 27, 2024. This has been corrected and the revised version was reposted on December 3, 2024.