Organic LETTERS
Letter
Cite This: Org. Lett. XXXX, XXX, XXX−XXX
pubs.acs.org/OrgLett

One-Pot Regioselective and Stereoselective Synthesis of *C*-Glycosyl Amides from Glycals Using Vinyl Azides as Glycosyl Acceptors

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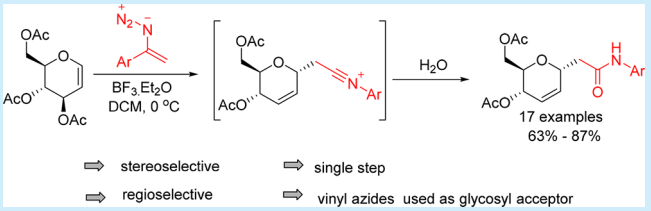
Supporting Information

ABSTRACT: The reaction of glycals containing good leaving groups with aromatic vinyl azides to give α-*C*-glycosyl amides in good yields is described. Various vinyl azides with different groups undergo the reaction smoothly. In these reactions, an iminodiazonium intermediate is generated by the attack of the vinyl azide onto the glycal under Lewis acid conditions. This undergoes Schmidt-type denitrogenative 1,2-migration to form a nitrilium ion, which, upon hydrolysis, gives the desired *C*-glycosyl amide.



C-Glycosides have gained widespread attention in recent years, because of their potential for use as inhibitors of carbohydrate-processing enzymes,[1−3] their metabolic stability compared to *O*-glycosides, and their applicability as intermediates in the synthesis of biologically important molecules.[4−9] This has led to a surge in the development of synthetic strategies for *C*-glycoside formation. Over the past few years, we have also tasted success in solving many of the problems faced in stereoselective *C*-glycosylation exploiting different glycosyl acceptors, such as boronic acids, unactivated alkynes, arylmethyl ketones, unactivated uracils, and benzenesulfonyl chlorides under palladium and Lewis acid catalysis.[10] Despite these advances, the vast diversity and distribution of *C*-glycosides, along with their unending medical applications, have left the subject of *C*-glycosylation open to further developments.

Small molecule screening libraries containing methylene amide linkages have resulted in the discovery of many chemical probes and drug leads in recent times.[11] *C*-Glycosides that have a methylene amide linkage as a part of the aglycon are no exception to this and are used as probes for a wide range of inheritable diseases and cardiovascular diseases.[12,13] For example, glycoside **I** (see Figure 1) activates the MAPKerk signaling pathways by up-regulating early response genes such as TRIB1 and LDLR, thereby leading to remarkable changes in lipoprotein metabolism. This results in a decrease in VLDL production and the upregulation of LDL uptake in cells of hepatic origin, thus having major implications in coronary artery disease.[12] However, the limited availability of these new chemical entities has restricted their study in biological targets. The chemical synthesis of such *C*-glycosides with methylene amide functionality requires multiple steps with late-stage amide linkage introduction, using the aminolysis of acids derived from esters (see Scheme 1a).[13−15] These conventional strategies have

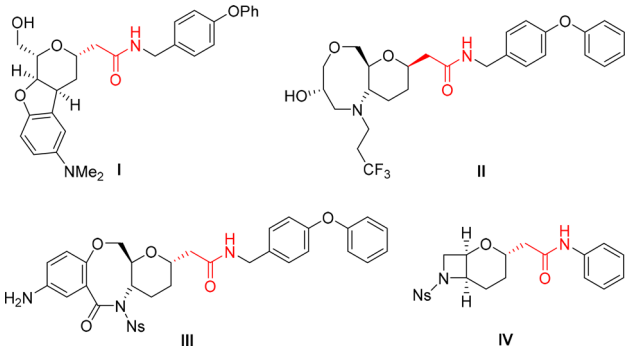


Figure 1. Biologically important *C*-glycosides having methylene amide linkage.

several other demerits, such as the use of BuLi in the generation of silylketene acetals as nucleophiles under cryogenic conditions and the lack of stereoselectivity (mixtures of α/β diastereomers) during the crucial glycosylation step, thereby leaving the scope for further modifications.

There is no report to date that involves a direct introduction of the amide functionality into the aglycon part during a *C*-glycosylation. In this respect vinyl azides, which can be easily derived from terminal alkynes,[16] are versatile substrates mainly used for nitrogen-containing molecules of importance in medicinal chemistry and materials science.[17] We envisaged (Scheme 1b) that, under Lewis acid activation, the anomeric carbon of the glycosyl donor might act as an electrophile in the formation of a C−C glycosidic bond with an enamine-type

Received: May 21, 2018

DOI: 10.1021/acs.orglett.8b01602
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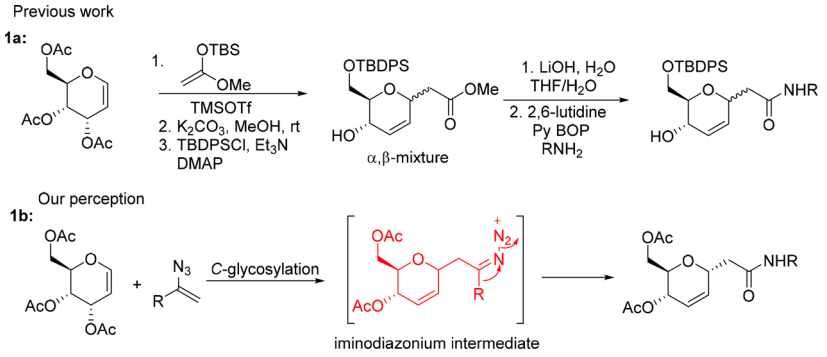
Scheme 1. Previous Report and Current Work



nucleophile generated from vinyl azide. This would form a glycosyl imino diazonium ion intermediate, which might undergo a Schmidt-type 1,2-migration to form nitrilium ion with the elimination of dinitrogen (N_2). Upon hydrolysis, we envisaged that this might produce glycosides bearing methylene amide linkages. As there is no report of using vinyl azides as glycosyl acceptors in *C*-glycosylation, and also considering the importance of the product, we took up the challenge of probing this as a one-step route to such *C*-glycosides.

In order to probe the potential of vinyl azides as glycosyl acceptors, tri-*O*-acetyl-D-glucal (**1**) and 3-chlorophenyl vinyl azide (**2**) were chosen. Initial reaction in the presence of TMSOTf at 0 °C gave a mixture of two products **1a** and **1b** in 1:2 ratio in 30% overall yield (see Table 1, entry 1), although

Table 1. Reaction of Tri-*O*-acetyl-D-glucal with 3-Chlorophenyl Vinyl Azide under Various Conditions[a]

entry	Lewis acid (equiv)	solvent	temperature (°C)	time (h)	yield[b] (**1a**:**1b**)
1	TMSOTf (1)	CH_2Cl_2	0	3	30 (1:2)
2	TMSOTf (1)	CH_2Cl_2	−20	4	40 (1:2)
3	TMSOTf (0.5)	CH_2Cl_2	−20	4	35 (1:2)
4	$InCl_3$ (0.5)	CH_2Cl_2	−20	4	20 (1:2)
5	$FeCl_3$ (0.5)	CH_2Cl_2	−20	4	30 (1:2)
6	CuOTf (0.5)	CH_2Cl_2	−20	4	30 (1:2)
7	$BF_3{\cdot}Et_2O$ (0.5)	CH_2Cl_2	−20	4	60 (2:1)
8	$BF_3{\cdot}Et_2O$ (1)	CH_2Cl_2	−20	4	70 (2:1)
9	$BF_3{\cdot}Et_2O$ (1.5)	CH_2Cl_2	−20	4	70 (2:1)
10	$BF_3{\cdot}Et_2O$ (1)	CH_2Cl_2	0	2	77 (1:0)
11	$BF_3{\cdot}Et_2O$ (2)	CH_2Cl_2	rt[c]	1	50 (1:0)

[a]In all cases, reactions were performed using **1** (1 equiv) and **2** (1.1 equiv). [b]Isolated yield after silica gel column chromatography. [c]Room temperature.

most of the starting material was consumed. Decreasing the temperature to −20 °C or the mole percentage of TMSOTf to 50% prevented the degradation of the starting material but there was no increase either in the yield or the proportion of **1a** in comparison to **1b** (Table 1, entries 2 and 3). In order to obtain **1a** as the sole product, the reaction was performed under various conditions, and the results are presented in Table 1. Screening of different solvents proved dichloromethane to be the best, giving predominantly **1a** in good yield (see the Supporting Information (SI), as well as Table 1). Use of 1 equiv of $BF_3{\cdot}Et_2O$ at 0 °C in DCM (Table 1, entry 10) proved to be the best conditions for this purpose.

The structure of the product **1a** was confirmed by spectroscopic analysis. Upfield chemical shift of the anomeric proton from δ 6.6 ppm to δ 4.6 ppm, together with the formation of new peaks at δ 2.5 ppm and δ 2.7 ppm in the ^{1}H NMR (400 MHz) of **1a** in $CDCl_3$, corresponding to two diastereotopic hydrogens of methylene carbon, clearly indicated the formation of a *C*-glycosyl amide. This was further confirmed by ^{13}C NMR spectroscopy which showed a new CH_2 peak at δ 40.8 ppm. The stereochemistry at the anomeric center was determined by two-dimensional nuclear magnetic resonance (2D NMR) (COSY, NOESY, HSQC, and HMBC). The NOESY spectrum of **1a** shows strong correlations between peaks of H1 and H6ab, as well as those of H5 and H7ab, but no correlation was found between signals of H1 and H5 (Figure 2), confirming the linkage at the anomeric center as α.

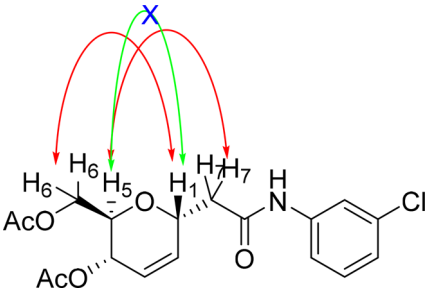
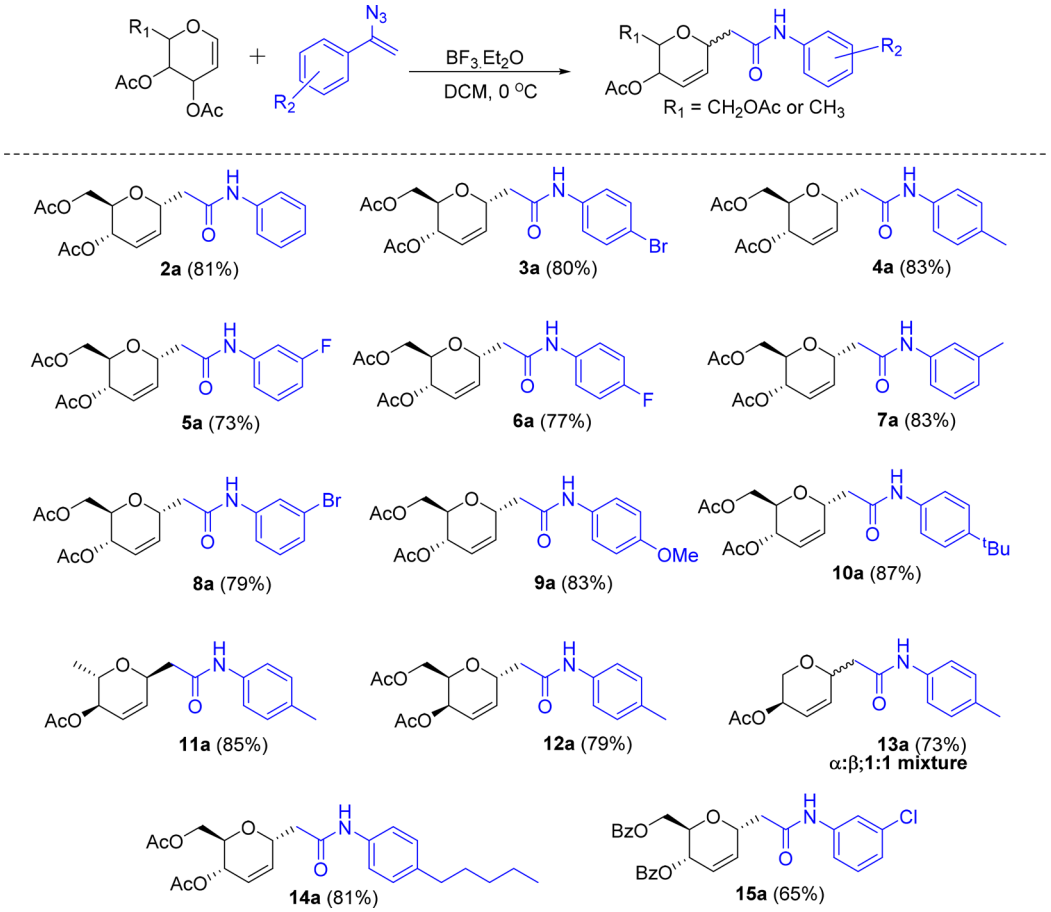


Figure 2. NOESY correlations of **1a**.

In order to check the substrate scope of the method, we performed the reaction of tri-*O*-acetyl-D-glucal with various vinyl azides under the optimized reaction conditions. In all cases, the reaction was found to proceed smoothly, affording the desired *C*-glycosyl amide in good to excellent yield with high stereoselectivity (see Scheme 2, entries 2a−15a). A variety of vinyl azides carrying aryl substituents possessing either electron-donating or electron-withdrawing groups were observed to undergo the reaction smoothly. Aryl rings having EDG groups at the *para* or *meta* positions gave the desired *C*-glycosyl amide in somewhat better yields, in comparison to substrates having EWG groups at any position. A series of other glycals (D-galactal, D-xylal, and L-rhamnal) were also examined under the standard reaction conditions. Both L-rhamnal and D-galactal provided the desired products with excellent stereoselectivity (see Scheme 1, entries 11a and 12a). However, in the case of D-xylal, a mixture of diastereomers ($\alpha\beta$, 1:1) was obtained. Other glycals with benzoyl protection reacted smoothly under the reaction conditions with 3-chloro vinyl azide to give the desired *C*-glycosyl amide (Scheme 2, entry 15a) while no reaction occurred with benzyl protecting groups, which resulted in hydrolysis of the vinyl azide itself.

DOI: 10.1021/acs.orglett.8b01602
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 2. Substrate Scope of *C*-Glycosyl Amides under Optimized Reaction Conditions[a]

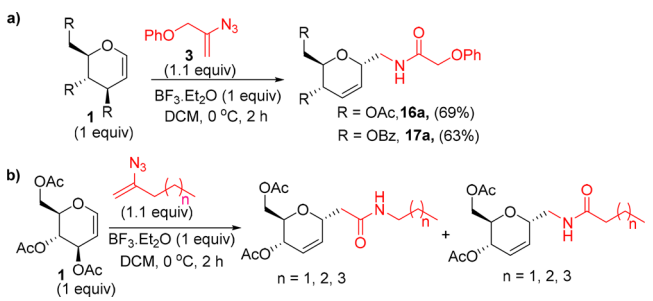


[a]Reaction conditions: To a solution of glycal (1 equiv) in CH_2Cl_2 (2 mL) was added $BF_3{\cdot}Et_2O$ (1 equiv) at 0 °C, followed by slow addition of the aryl vinyl azide (1.1 equiv) at the same temperature and maintained for 2 h. Values given in parentheses indicate isolated yields after silica gel column chromatography.

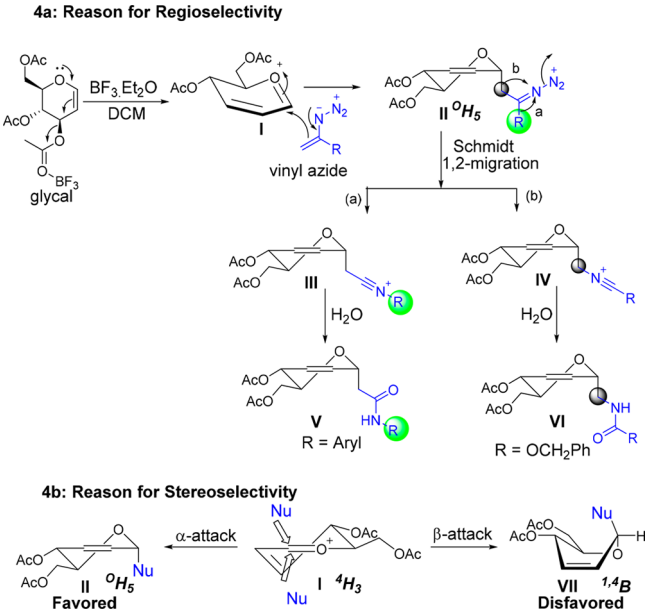
In order to expand the substrate scope of the reaction, the reactivity of vinyl azides derived from aliphatic alkynes as glycosyl acceptors was examined. Interestingly, a vinyl azide having an α-methylene phenoxy group (**3**) under a similar set of reaction conditions reacted differently to produce *C*-glycosyl amides (Scheme 3a, entries 16a and 17a) bearing a $CH_2{-}NH{-}COPh$ instead of a $CH_2{-}CO{-}NHPh$ as exclusive products. However, an inseparable mixture of two regioisomers was obtained from vinyl azides having long carbon chains (Scheme 3b).

A possible mechanism for the reaction is shown in Scheme 4. The formation of oxacarbenium ion (**I**) from glycal in the

Scheme 3. Reaction of Tri-*O*-acetyl-D-glucal with Various Aliphatic Vinyl Azides under Optimized Reaction Conditions



Scheme 4. Plausible Mechanism for the Formation of *C*-Glyoside Amides from Glycals and Vinyl Azides



DOI: 10.1021/acs.orglett.8b01602
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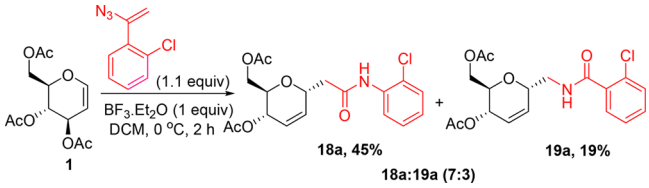
presence of $BF_3{\cdot}Et_2O$ is followed by the nucleophilic attack of vinyl azide from the bottom face to form an iminodiazonium intermediate (**II**), which undergoes Schmidt-type 1,2-migration with elimination of dinitrogen to form the nitrilium ion **III** or **IV**. Upon hydrolysis, this gives corresponding amides **V** or **VII**, depending on the migratory aptitude of the substituents. The regioselectivity of the reaction is decided at this stage. Groups such as aryl, which have higher migratory aptitude than the sugar, take pathway (a) to form the nitrilium ion **III**, while α-methylene phenoxy groups, having lower migratory aptitude than the sugar, take the other route (b) to form intermediate **IV**. In the case of the groups that have comparable migrating ability, a mixture of two regioisomers is obtained as observed in the case of vinyl azides having long carbon chains. Indeed, while working with *ortho*-chlorophenyl vinyl azide (Scheme 5), we were able to isolate and characterize both the regioisomers **18a** (major) and **19a** (minor) in a 7:3 ratio.

Scheme 5. Reaction of Tri-*O*-acetyl-D-glucal with Orthochlorophenyl Vinyl Azide



Based on our experimental results, the migratory aptitude of the different groups is Ar ≫ CH_2−sugar = $-(CH_2)_n-CH_3$ (n > 2) > CH_2OPh. The stereoselectivty at the anomeric center is governed by conformational effects (Scheme 4b), where the α-attack is favored because it leads to the energetically more favorable half-chair conformation $^{O}H_5$ (**II**), compared to β-attack, which results in energetically less favorable high-energy boat conformation $^{1,4}B$ (**VII**).[18]

In conclusion, we have developed an efficient method for the synthesis of *C*-glycosides using vinyl azides as enamine-type nucleophilic reagents. For the first time, vinyl azides have been used as glycosyl acceptors in a *C*-glycosylation. The synthesis of *C*-glycosides proceeded stereoselectivily giving only the α-anomer as a single product. The glycosylation proceeds with the formation of a single *C*-glycosyl amide product with most aryl vinyl azides. We anticipate that the present method can be readily adapted for the synthesis of biologically and medicinally important amide-containing *C*-glycosides.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01602.

Experimental procedures, ^1H and ^{13}C NMR spectra, and characterization of all compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors are thankful to DST-India for funding uner the project GAP-2155 and under INSPIRE faculty programme (IFA-11-CH-18, GAP-1179). F.R and N.H thank CSIR-New Delhi and UGC-New Delhi for senior research fellowships. A.A thanks CSIR-New Delhi for junior research fellowship. IIIM Publication No. IIIM/2221/2018.

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DOI: 10.1021/acs.orglett.8b01602
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