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Synthesis of Structurally Diverse Substituted Aziridinyl Glycoconjugates via Base-Mediated One-Pot Post-Ugi Cyclization

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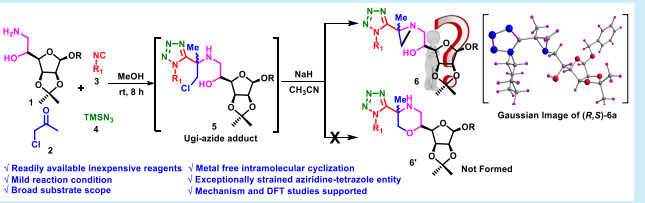
Supporting Information

ABSTRACT: The base-promoted intramolecular cyclization of Ugi-azide adduct has been demonstrated for the synthesis of highly substituted aziridinyl glycoconjugates in one pot. The reactions are scalable and efficient and have an operationally simple broad substrate scope. To gain insight into the mechanism of aziridine formation, DFT and control experiments show that the cyclization of the aziridine glycoconjugate pathway was preferred, as it proceeds with a low activation energy barrier (0.57 kcal mol^{-1}), which supports our experimental observation.



In organic chemistry the smallest nitrogen-containing heterocycle motif, aziridines, constitutes a highly interesting synthetic building block as well as an important synthetic target.[1] Ring strain of these spring-loaded heterocycles provides a distinctive advantage as it can be used as a precursor for the synthesis of more complex molecules.[2] Together, the biological activity displayed by the aziridine ring containing natural compounds (Figure 1) makes them a

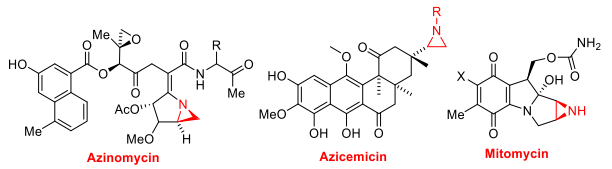


Figure 1. Bioactive compounds containing an aziridine core.

prudent choice in synthesizing novel molecules. Introducing aziridine rings as sugar derivatives is also quite significant and indispensable[3] in the area of glycobiology.

For expanding the field of glycoscience, it is essential to synthesize biologically relevant oligosaccharides, glycoconjugates, glycomimetics, and other analogues.[4−6] For example, Hou et al. reported that the intramolecular aziridination followed by reductive ring opening provided the synthesis of immunostimulant, the 4′-epimer of α-CGalCer.[7]

With considerable interest and extensive research, chemical N-functionalization[8] of carbohydrate derivatives with amine substitution will be a suitable option due to their potential bioactivity as well as the synthetic challenges.[9] Therefore, new synthetic approaches for the construction of aziridine moieties are an important research area. Currently available synthetic methodologies[10] involve (a) transfer of a suitable nitrogen source to olefins, (b) transfer of a suitable carbon source to imines, and (c) intramolecular cyclization of chiral 1,2-vicinal haloamines or amino alcohol derivatives. The literature on aziridine synthesis via intramolecular cyclization is dominated by the Wei[11a] and Jacobsen group,[11b] who reported the preparation of stereoselective aziridines. Furthermore, Hayashi and co-workers[12] developed a one-pot synthesis of enantioenriched aziridines having a β-hydroxyethyl moiety using diaryl prolinolsilyl ether. Similarly, Bartoli et al.[13] developed a one-pot procedure for enantioenriched N-Boc-protected aziridine synthesis using the Co(III)−Salen catalyst.

On the other hand, the development of synthetic methods for rapid access to N-functionalization with complexity and diversity, through multicomponent reactions (MCRs), is an eye-catching area to access biologically and pharmaceutically important complex molecules. Apart from the synthesis of several established strategies, the preparation of highly substituted aziridinyl glycoconjugates is attracting immense interest.

Despite all these facts, the efficient synthesis of highly substituted aziridines from glycosyl amino alcohols has not yet been attempted. In view of these, in the current work, we have successfully demonstrated the novel usefulness of isocyanide-based multicomponent Ugi[14] reaction followed by post-intramolecular S_N2 cyclization for the construction of highly substituted aziridinyl glycoconjugates. We identified a class of a three-membered strained ring, highly substituted aziridinyl glycoconjugate product, signifying the unique reactivity associated with glycosyl amine (Scheme 1). To the best of our knowledge, herein we report for the first time the synthesis

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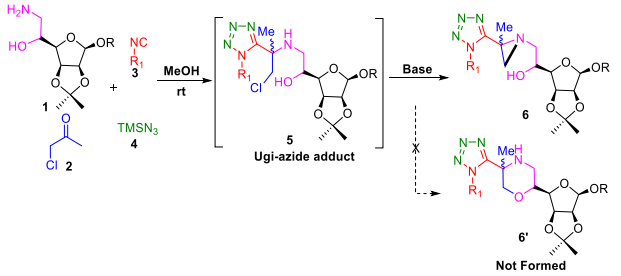
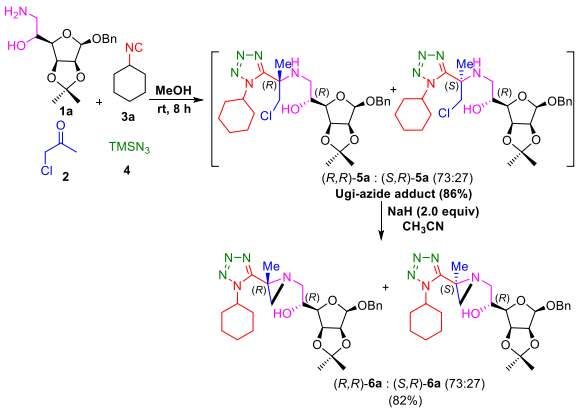
Scheme 1. Strategies for the Synthesis of Substituted Aziridinyl Glycoconjugates from Glycosyl Amino Alcohols



of structurally diverse strained aziridinyl glycoconjugates via a one-pot Ugi-cyclization procedure from functionalized glycosyl amino alcohols.

In this study we employed the Ugi reaction by reacting with suitable glycosyl amino alcohol (**1a**, 1.0 equiv) and chloroacetone (**2**, 1.0 equiv) in the presence of cyclohexyl isocyanide (**3a**, 1.0 equiv) and TMS-N_3 (**4**, 1.0 equiv) in methanol at room temperature to access the corresponding Ugi-azide adduct **5a** as a diastereomeric mixture (product ratio 73:27) in good 86% yield (Scheme 2, also see the Supporting

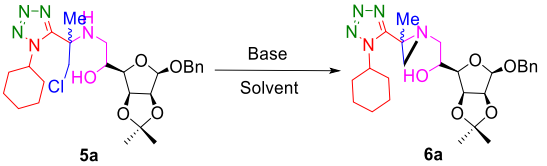
Scheme 2. MCR for the Ugi-Azide Adduct 5a and Synthesis of Strained Aziridinyl Glycoconjugates 6a



Information (SI)).[15] However, diastereomers were separated on the column by slow elution, with (*R*,*R*)-**5a** eluting first and (*S*,*R*)-**5a** later. The exact structure of **5a** and stereochemistry at the new stereogenic center were unequivocally established by carrying out extensive NMR studies, especially by analyzing the NOEs and ^3J scalar coupling constant values (for details, please see SI, Figure-S1). The top 20 minimum energy conformations, from the 1nS restrained molecular dynamic simulations, were superimposed and represented in Figures S6 and S7.

Then we proceeded further to the intramolecular cyclization with Ugi-azide adduct **5a**, in the presence of NaH and dry DMF. However, we only observed 52% product formation (Table 1, entry 1). The ^{1}H NMR spectrum of the resulted product **6a** was showing a singlet at δ 2.18 and δ 1.87 ppm corresponding to one proton each, which was present on the carbon at δ 32.3 ppm (please see SI). However, it was rather surprising to see the geminal protons having a ^2J coupling constant value as zero. The small value or zero geminal coupling constants are rare and reported for strained ring systems such as 3-membered rings.[16] In order to elucidate the structure of the product formed from intramolecular

Table 1. Optimization of Cyclization of the Ugi-Azide Adduct to the Aziridinyl Glycoconjugate[a]



entry	base	equiv	temp (°C), time	solvent	yield[a] (%)
1	NaH	2	0−rt, 1 h	DMF	52
2	NaH	2	0−rt, 1 h	THF	53
3	**NaH**	**2**	**0−rt, 45 min**	**CH_3CN**	**82**
4	NaH	2	0−rt, 5 h	CH_3CN	72
5	Et_3N	2	rt, 24 h	CH_3CN	-
6	DIPEA	2	rt, 24 h	CH_3CN	-
7	DBU	2	rt, 24 h	CH_3CN	-
8	DABCO	2	rt, 24 h	CH_3CN	-
9	K_2CO_3	2	rt, 24 h	CH_3CN	49
10	KOH NaOMe	2	rt, 24 h	CH_3CN	42
11	*t*-BuOK	2	rt, 24 h	CH_3CN	44
12		2	rt, 24 h	CH_3CN	66

[a]General conditions: **1a** (1.0 mmol), **base** (2.0 equiv), solvent (2.0 mL). [b]Isolated yield after silica gel column chromatography.

cyclization, we have carried out extensive NMR analysis employing both homo- and heteronuclear 2D experiments. HMBC correlations of C_6H (δ 3.02 and δ 2.45 ppm) with C_7 (δ 40.45 ppm), C_7H (δ 2.18 and 1.87 ppm), with C_6 (δ 55.28 ppm), CIII (δ 32.3 ppm), and CIV (δ 155.54 ppm) supported the formation of the aziridine ring unequivocally (for details, please see SI, Figures S2, S3, and S4). Due to its highly strained nature, aziridine ring formation was not favorable; instead, one would expect the formation of a less strained 6-membered morpholine glycoconjugate **6′**. However, we have not observed even a trace amount of the O-alkylated product (**6′**). The Ugi-azide adduct generated *in situ* underwent a more favored 3-exotet cyclization, leading to the aziridinyl glycoconjugate formation, due to the excess nucleophilic nature of the secondary amine than the hydroxyl group.

Further, we attempted to improve the yield of **6a** (which was only 52% in NaH, DMF), and for the optimization studies we have treated **5a** with a variety of solvents, bases, and temperature and at different reaction time periods as well (Table 1). As a result from the optimization of reaction conditions, it was identified that acetonitrile was the most suitable solvent for cyclization in comparison with other solvents such as THF and DMF (Table 1, entries 1−3). In addition, we have also explored the impact of various organic bases using triethyl amine, DIPEA, DBU, DABCO, as well as inorganic bases like K_2CO_3, KOH, NaOMe, *t*-BuOK, and NaH on the overall yield of the reaction. No product formation was observed in the case of organic bases (Table 1, entries 5−8), but in the presence of K_2CO_3, KOH, NaOMe, and *t*-BuOK, there was no improvement in the yield of the desired product **6a** (Table 1, entries 9, 10, 11, and 12), even after longer reaction time periods. Therefore, we deduced that the reaction carried out in sodium hydride (82% yield) and acetonitrile for 45 min at 0 °C to rt was proven to be an excellent choice for the cyclization (Table 1, entry 3).

Once the synthesis of aziridinyl glycoconjugate **6a** was achieved in good yields, we further explored the scope and generality of the reaction for the synthesis of different Ugi-

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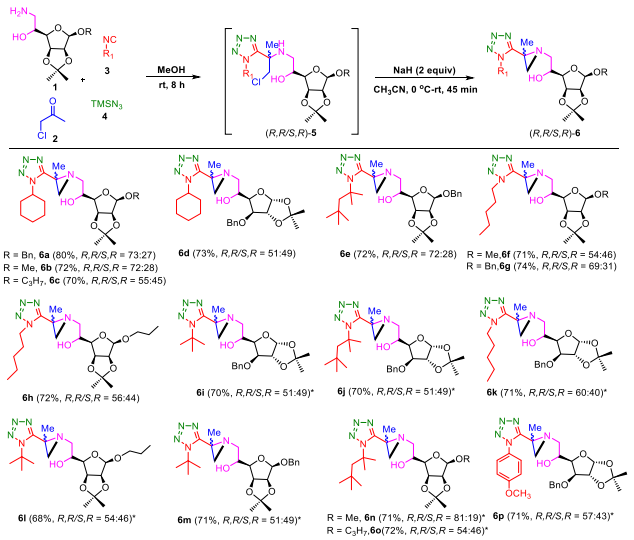
azide adducts (see SI Scheme S4). In this regard, the effect of the furanose form of mannose and glucose amino alcohols with various protecting groups was also investigated, where both of these functionalities were unaffected and found in general moderate to good yields of Ugi-azide adducts.

To further simplify the synthesis, we turned our attention to propose a one-pot Ugi-cyclization procedure for the synthesis of highly substituted aziridinyl glycoconjugates. We planned to remove the Ugi solvent methanol after formation of **5a** without purification, followed by the addition of NaH in acetonitrile at 0 °C to rt for 45 min (under optimized reaction conditions, Table 1, entry 3). We have obtained the exclusively aziridinyl glycoconjugates (**6a**) in 80% yield with no trace amount of the O-alkylated product. Encouraged by this remarkable one-pot protocol, we tested various isocyanides and glycosyl amino alcohols and found in general moderate to good yields of highly substituted aziridinyl glycoconjugates (Scheme 3).

Scheme 3. One-Pot Ugi-Cyclization for the Synthesis of Aziridinyl Glycoconjugates[a,b]



[a]General conditions: To a solution of chloroacetone **2** (1.0 equiv) in methanol (1M) at room temperature were added glycosyl amino alcohols **1a–d** (1.0 equiv), isocyanide **3** (1.0 equiv), and trimethylsilylazide (2.0 equiv). [b]One-pot overall isolated yield. Diastereoisomeric ratio was determined by ^{1}H NMR analysis. *Not separated isomers.

However, there were some questions to address: First, the deprotonation takes place either from the hydroxyl group or from the NH group or both. Second, how does the substitution of chlorine occur? Third, does the aziridine ring form exclusively or will there be any formation of the O- alkylated product? In order to investigate the reaction mechanism, the cyclization step was monitored by acquiring a series of ^{1}H NMR spectra (Figure 2).

In the NMR sample tube, initially we have dissolved the Ugi-azide adduct **5a** in deuterated CD_3CN and acquired a proton spectrum which is represented as stage-1 in Figure 2.

Then, after we have added 1 equiv of NaH to the mixture incubated at 0 °C. After 5 min of incubation, the proton spectrum was acquired, and it was observed that the peak of OH disappeared. We also have noticed that the NH peak was intact (stage-2). However, there is no formation of O-alkylated product even after longer time. Further, when one more equiv

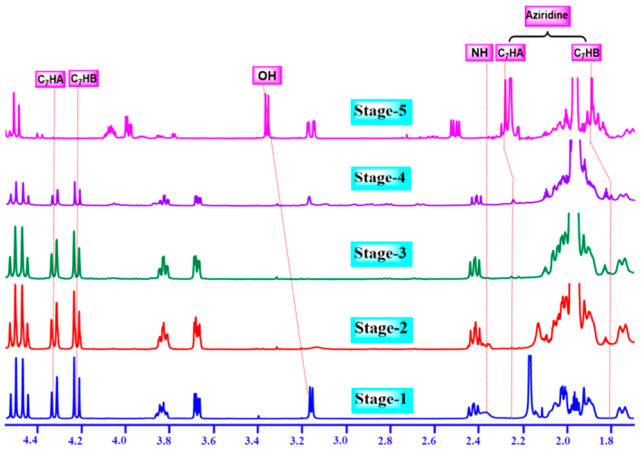


Figure 2. Section of ^{1}H NMR spectra of the cyclization step.

of NaH was added and after 15 min, both the protons of OH and NH disappeared (stage-3), without any formation of the product. However, after 25 min of incubation at room temperature, we observed that the signal intensity of the peaks corresponding to the starting material started diminishing for, e.g., peaks of C_{7HA} and C_{7HB} at δ 4.32 and δ4.21 ppm, respectively, and simultaneously we noticed the appearance of a new set of singlets at δ 2.16 and δ 1.81 ppm (stage-4). Incubation was continued, and after 45 min, we noticed complete disappearance of C_{7HA} and C_{7HB} (δ 4.32 and δ 4.21 ppm) of the starting material, which then resonated at δ 2.16 and δ 1.81 ppm, clearly indicating the formation of an N-alkylated aziridine ring. We also noticed the appearance of the OH proton in stage-5. From these experiments, it clearly demonstrates that the deprotonation of the OH takes place first followed by the deprotonation of the NH proton. The intramolecular cyclization takes place through amine forming the strained 3-membered aziridine ring rather than the 6-membered morpholine ring (Figure 3). To validate the experimental results toward the formation of cyclized aziridine glycoconjugates, DFT calculations were performed using G09, Gauss view program. The cyclization of aziridinyl glycoconju-

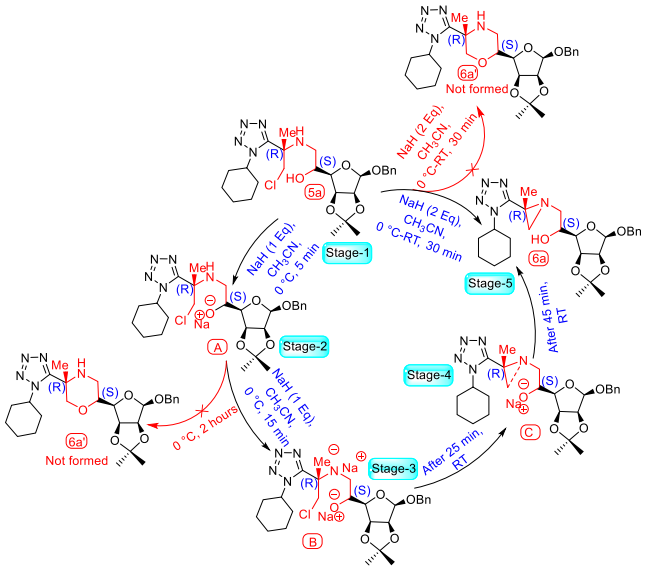


Figure 3. Possible mechanism depicted by NMR study.

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gate proceeds with low activation energy compared to the morpholine cyclization pathway (please see the SI, Figure S5).

In conclusion, we have shown a general one-pot post-Ugi cyclization reaction as an innovative synthetic method for the synthesis of carbohydrate-derived highly strained substituted aziridine. This robust and operationally simple two-step, air- and moisture-tolerant procedure furnished fast-track strategy with various advantageous features including synthesis of highly strained complex molecules from simple starting materials. This small nitrogen-containing building block is imposed by complexity involved in the synthesis due to the ring strain that makes them useful precursors in the fields of synthetic and medicinal chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00862.

Detailed experimental procedures, complete characterization data, DFT calculation and copies of NMR spectra. The authors declare no competing financial interest (PDF)

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Notes

The authors declare no competing financial interest.

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