Urea Glycoside Synthesis in Water

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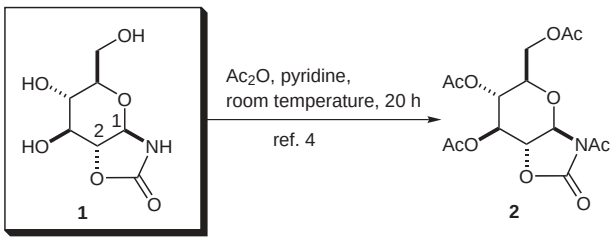
Abstract: A novel approach to the synthesis of urea glycosides in aqueous media has been developed. Reaction of Steyermark's glucosyl carbamate **1** with amines was carried out in water to afford urea glucosides in good yields. This method was successfully applied to develop a new route to the synthesis of urea-tethered neoglycoconjugates and pseudooligosaccharides.

Key words: carbohydrates, glycosylations, glycosides

Urea glycoside is found in nature as a unique structural motif of glycocinnamoylspermidine antibiotics,[1] and several years ago, we initiated work on the synthesis of this class of amino sugar antibiotics. Parallel to this synthetic effort for the natural products, we also paid attention to the urea-tethered neoglycoconjugates and pseudooligosaccharides. While several synthetic routes to the urea glycoside had been reported, they appeared to be not suitable for our purpose with respect to the functional group compatibility and stereoselectivity.[2] Accordingly, we developed new synthetic protocols which involve the reaction of glycopyranosyl isocyanate with amines under anhydrous conditions in organic solvents.[3] During this investigation, we felt it necessary to explore urea glycoside synthesis which utilizes unprotected sugars in water. We envisioned that such an approach would be useful for bioconjugate synthesis under physiological conditions, because most parts of biomolecules are soluble in aqueous solution.

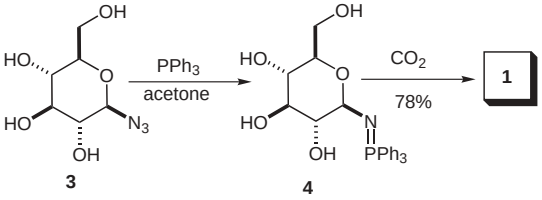
After surveying the chemical literature, we were most interested in the anomalous reactivity of a glucose derivative **1** bearing 1β,2α-oxazolidone ring (Scheme 1). The first synthesis of **1** was reported in 1962 by Steyermark, who observed that acetylation of **1** (Ac_2O, pyridine, r.t., 20 h) occurred on both the hydroxyl groups and nitrogen in carbamate ring to afford the tetraacetate **2**.[4]



Scheme 1

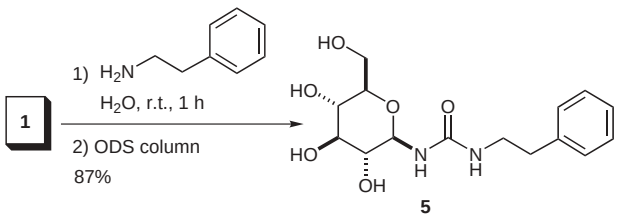
Since usual carbamates do not undergo acetylation under such mild reaction conditions,[5] the highly reactive nature of **1** can be attributed to its twisted structure, in which overlap of the lone pair on the nitrogen atom with the system of the carbonyl group is prevented by the rigid geometry of **1**. Consequently, it is expected that ring-opening reaction of **1** with nucleophiles is prone to occur with a decrease in ring strain.[6] In fact, Pinter reported, albeit only one example, the reaction of **1** with *N*-methylpiperazine in water to afford urea glucoside.[7] Herein we report the synthetic potential of this Steyermark's carbamate **1** for the preparation of urea-tethered neoglycoconjugates and pseudooligosaccharides in aqueous media.

Steyermark's carbamate **1** was prepared from glucosyl azide **3** according to the procedure of Pinter (Scheme 2).[8] The Staudinger reaction of β-D-glucopyranosyl azide **3** with triphenylphosphine in acetone gave a solution of phosphinimine **4**, which was successively treated with carbon dioxide in one-pot process. The precipitate was collected to furnish **1** in 78% yield.



Scheme 2

Initially, we examined the reaction of **1** with 2-phenylethylamine, because the product could be readily purified by reverse phase chromatography (Scheme 3). The ring-opening reaction of **1** with 2-phenylethylamine in water occurred smoothly at room temperature for one hour, and the urea glucoside **5** was isolated in 87% yield after ODS (Cosmosil® $75C_{18}$-OPN) column chromatography.



Scheme 3

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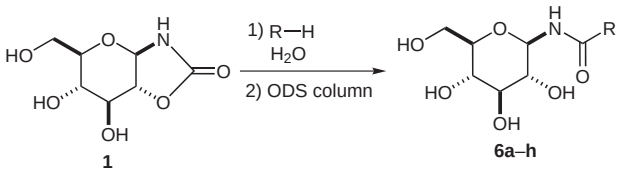
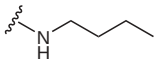
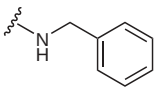
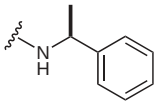
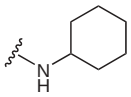
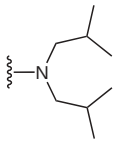
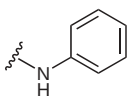
In order to evaluate the reactivity of **1** and to identify the steric factors of the alkyl group in amine, the reaction of **1** with a variety of amines was examined using reaction conditions similar to those employed in Scheme 3. Results are summarized in Table 1.

Primary amines, *n*-butylamine and benzylamine, having no branches at the α-carbon reacted with **1** to afford the urea glucosides **6a** and **6b** in good yields (entries 1 and 2). Alkyl substituents at the α-position of primary amine had a considerable steric effect (entries 3 and 4). Thus, reaction of (*S*)-(–)-α-methylbenzylamine and cyclohexylamine with **1** (1.2 equiv) afforded the products **6c** and **6d** in moderate yields (67% and 68%). Slightly more carbamate **1** (1.5 equiv), longer reaction time (1.5 h) and keeping the reaction mixture at 40 °C (entry 4) improved the yields (80% and 84%). With secondary amines (entries 5 and 6), use of 2.0 equivalents of **1** gave the products **6e** and **6f** in 80% and 71% yields. The difference between entries 5 and 6 can be rationalized by the fact that because of its cyclic structure, pyrrolidine has lone-pair electrons that are more accessible for nucleophilic ring-opening reaction than those of diethylamine. The steric effect at the β-position of secondary amine considerably reduces the

Table 1 Results of the Reaction of Carbamate **1** with a Variety of Amines

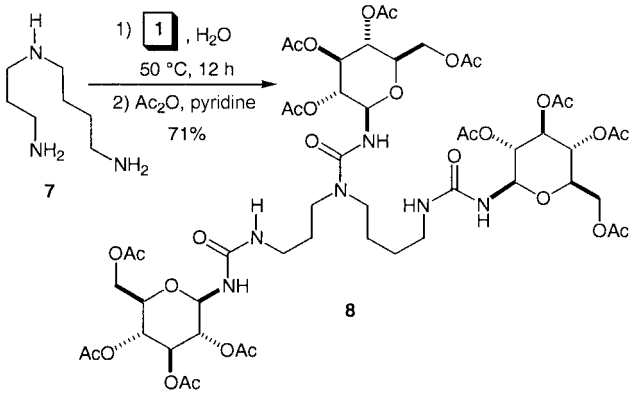


Entry	Product (R =)	Time (h)	Temp (°C)	Equiv of **1**	Yield (%)[a]
1	 **6a**	1.0	r.t.	1.2	93[b]
2	 **6b**	1.0	r.t.	1.2	88
3	 **6c**	1.0 2.0	r.t. r.t.	1.2 1.5	67 80
4	 **6d**	1.0 2.0	r.t. 40	1.2 1.5	68 84
5	 **6e**	3.0	60	2.0	80[c]
6	 **6f**	6.0	50	2.0	71[b]
7	 **6g**	12	50	2.0	8
8	 **6h**	12	70	1.5	75

[a] Unless otherwise noted, yields were calculated after ODS column purification.
[b] Since the product is hygroscopic, the yield was determined after acetylation.
[c] The product was isolated after acetylation, because purification by ODS column was difficult.

yield. For example, when diisobutylamine was employed (entry 7), only 8% of **6g** was isolated. Aniline (entry 8) underwent urea glycosylation in water at 70 °C for 12 hours to furnish **6h** in 75% yield. In this case, raising the reaction temperature did not accelerate the hydrolysis of **1** due to the weaker basicity of aniline.

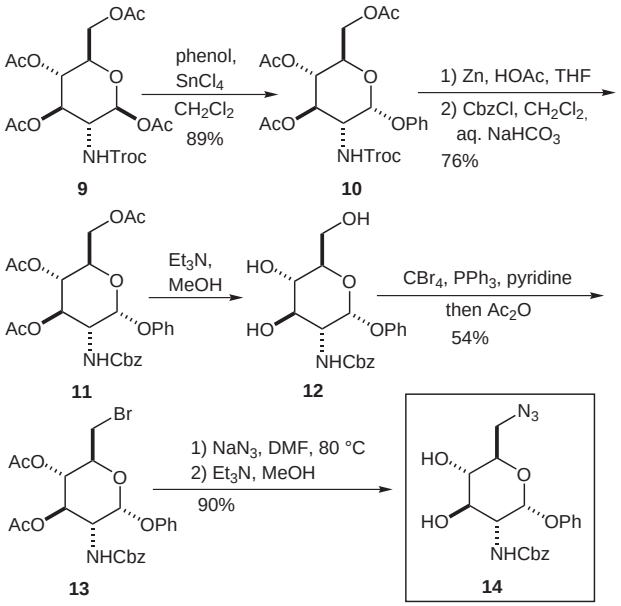
Given the encouraging results stated above, we next turned our attention to develop a bioconjugation method using **1**, and a preliminary example is illustrated in Scheme 4. Spermidine (**7**) underwent urea-glycosylation with **1** in water, and the corresponding urea glycoside **8** was isolated after acetylation in 71% yield.[9]



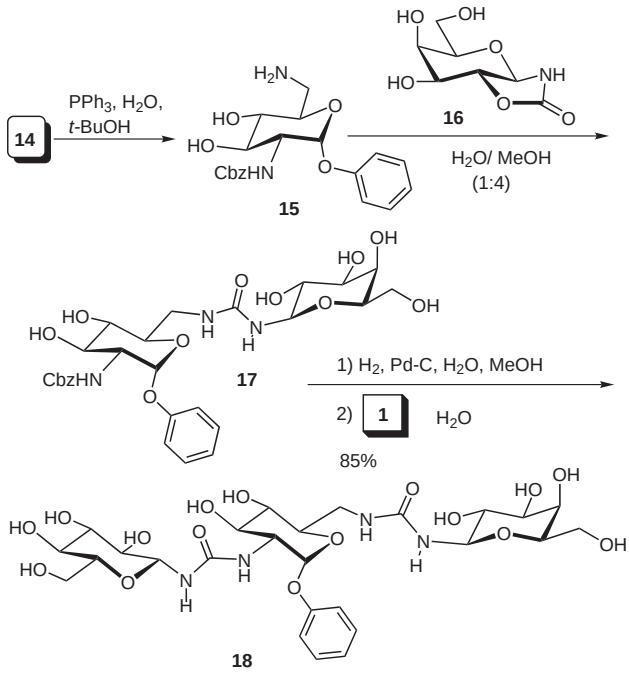
Scheme 4

Finally, we undertook the synthesis of urea-linked oligosaccharide mimics[11] in aqueous solvents. For this purpose, we set up to prepare phenyl 2,6-diamino-glucopyranoside (**14**), which bears two reactive sites for the reaction with carbamates (Scheme 5). Phenyl group in **14** was planned to facilitate the final purification step with ODS column chromatography. Glycosylation of glucosamine derivative **9** with phenol, catalyzed with tin(IV) chloride in dichloromethane, proceeded smoothly to afford α-phenyl glycoside predominantly in 89% yield.[10] Treatment of **10** with zinc in a mixture of HOAc and THF removed Troc carbamate to afford the corresponding amine, which was immediately reprotected to its Cbz-derivative **11** in 76% yield for two steps. Cleavage of acetyl groups in **11** (Et_3N, MeOH) gave the triol **12**. Selective bromination (CBr_4, PPh_3, pyridine) of the primary hydroxyl group in **12** and acetylation (Ac_2O added in one pot) furnished bromide **13** (54% in two steps). Displacement of the bromide **13** with sodium azide in DMF and methanolysis of the acetate groups (Et_3N, MeOH) afforded **14**, which was employed as precursor in the synthesis of an urea-linked pseudotrisaccharide **18** (Scheme 6).

The synthesis of **18** began with the reduction of azide **14** with triphenylphosphine. The resultant amine **15** underwent urea-glycosylation with galactopyranosyl carbamate **16** in aqueous media (H_2O/MeOH, 1:4) to afford pseudodisaccharide **17**. Deprotection of the Cbz group in **17** gave the corresponding 2-amino-pseudodisaccharide, which



Scheme 5



Scheme 6

was subsequently treated with **1** in water. The resultant product was purified by ODS chromatography to furnish **18** in 85% overall yield for four steps.

In conclusion, we have demonstrated that Steyermark's carbamate is a useful synthon for the synthesis of urea-tethered neoglycoconjugates and pseudooligosaccharides in aqueous media. This approach represents a useful protocol for anchoring a carbohydrate moiety onto an amine in water, which may mimic the enzyme-catalyzed glycosylation in water.

General Procedure of Urea-Glycosylation in Water. To a solution of phenethylamine (54 mg, 0.45 mmol) in H_2O (10.0 mL) was added carbamate **1** (110 mg, 0.54 mmol) in a single portion. After stirring at r.t. for 1.0 h, the reaction mixture was directly passed through a column of ODS (Cosmosil® C_{18}-OPN, H_2O followed by H_2O/MeOH, 10:1 as eluent). The urea glucoside **5** was obtained as a white solid (126 mg, 87%).[12]

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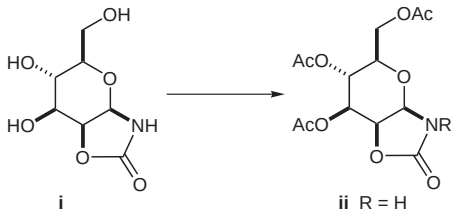
(5) For mannose type, carbamate **i** underwent acetylation (Ac_2O, pyridine, r.t.) to afford triacetate **ii**. Acetylation of **i** under more forcing conditions (Ac_2O, NaOAc, refluxed for 1 h) gave *N*-acetate **iii** (Scheme 7). See the reference: Kovacs, J.; Pinter, I. *Carbohydr. Res.* **1991**, *210*, 155.



Scheme 7

(6) For the reactivity of strained carbamates, see the reference: Hall, H. K. Jr.; El-Shekeil, A. *J. Org. Chem.* **1980**, *45*, 5325.

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(9) The separation of glucose, hydrolyzed product of **1**, by ODS column was difficult in this case.

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(11) For recent examples of the pseudooligosaccharides with thiourea linkage, see: Jiméne Blanco, J. L.; Bootello, P.; Ortiz Mellet, C.; Gutiérrez Gallego, R.; García Fernández, J. M. *Chem. Commun.* **2004**, 92.

(12) Spectroscopic data of **5**: ^{1}H NMR (400 MHz, CD_3OD): δ = 2.77 (2 H, t, *J* = 7.0 Hz), 3.13 (1 H, t, *J* = 9.0 Hz), 3.25 (1 H, t, *J* = 9.0 Hz), 3.32 (1 H, ddd, *J* = 9.0, 5.5 and 2.0 Hz), 3.37 (2 H, t, *J* = 7.0 Hz), 3.38 (1 H, t, *J* = 9.0 Hz), 3.63 (1 H, dd, *J* = 12.0 and 5.5 Hz), 3.81 (1 H, dd, *J* = 12.0 and 2.0 Hz), 4.73 (1 H, dd, *J* = 9.0 Hz), 7.15–7.29 (5 H). ^{13}C NMR (100 MHz, CD_3OD): δ = 37.3, 42.6, 62.8, 71.6, 74.3, 79.1, 79.2, 82.8, 127.3, 129.5, 129.8, 140.7, 160.5.