Synthesis of Urea and Carbamate Glycosides Employing Unprotected Carbohydrates

Yoshiyasu Ichikawa,* Shohei Kusaba, Takahiro Minami, Yumiko Tomita, Keiji Nakano, Hiyoshizo Kotsuki

Faculty of Science, Kochi University, Akebono-cho Kochi, 780-8520, Japan
Fax +81(88)8448359; E-mail: ichikawa@kochi-u.ac.jp

Received 9 March 2011

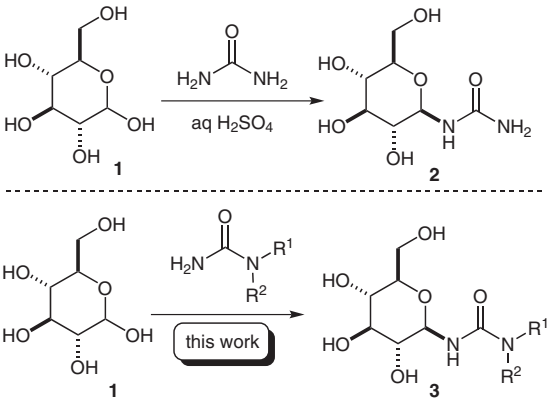
Abstract: A study of methods for the synthesis of urea and carbamate glycosides, starting with unprotective carbohydrates, led to the preparation of amino acid–carbohydrate conjugates in aqueous media.

Key words: neoglycoconjugates, urea, carbamate, glucose, glucosamine

The fundamental importance of glycoconjugates in a wide range of biological processes has promoted a great deal of interest in neoglycoconjugates as tools for glycobiology as well as potential therapeutic agents.[1] Our efforts in this area have focused on the synthesis of neoglycoconjugates, in which the *O*- and *N*-glycosyl linkages are replaced with urea–glycosyl bonds.[2] Our specific interest in urea-tethered neoglycoconjugates arose during the synthetic works of the amino sugar antibiotic, glycocinnasperimicin D, which possesses a urea glycoside as a key structural unit.[3]

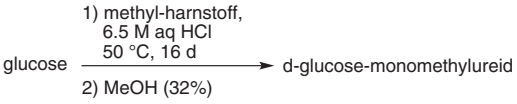
Although a number of new synthetic methods to access urea glycosides have been developed by us[4] and others[5] the existing procedures have the drawback in their low efficiency, particularly due to the length of the synthetic routes arising from extensive use of protection/deprotection sequences. In this context, we became intrigued by a classical method for the synthesis of urea glucoside **2**, which involves acid-catalyzed condensation of D-glucose (**1**) with urea[6] (Scheme 1). This simple process is remarkable, because urea glucoside **2** is formed from protecting-group-free D-glucose. Stimulated by the synthetic potential of this reaction as a method for urea-tethered neoglycoconjugate synthesis, we launched an investigation to extend this process to the synthesis of N-substituted urea glycosides **3**.

After extensive literature browsing, we found that few precedents exist for the reaction of N-substituted urea derivatives with carbohydrates. In 1926, Helferich reported the reaction of glucose with methyl-harnstoff (1-methylurea) in aqueous HCl at 50 °C for 16 days leading to the production of D-methylurea glucoside (d-glucose-monomethylurid)[7] (Scheme 2). Following this work, Erickson investigated the reaction of long-chain octadecylurea with D-glucose.[8] Although these two early reports described the synthesis of N-substituted urea glucosides,



Scheme 1 Urea glycoside synthesis plan

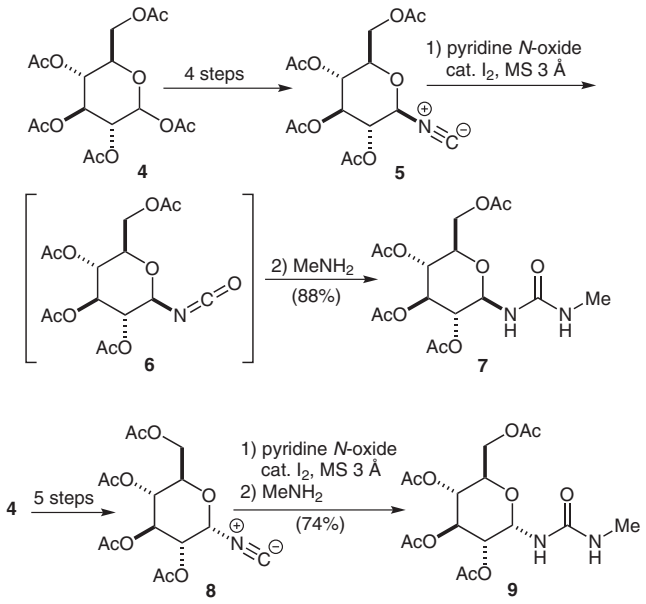
products were characterized only by melting points, elemental analyses and optical rotations. Importantly, the structures of the products of these processes have never been elucidated completely. In addition, the yields are quite low, and the stereochemistry of the products (α/β selectivity) has not been determined.



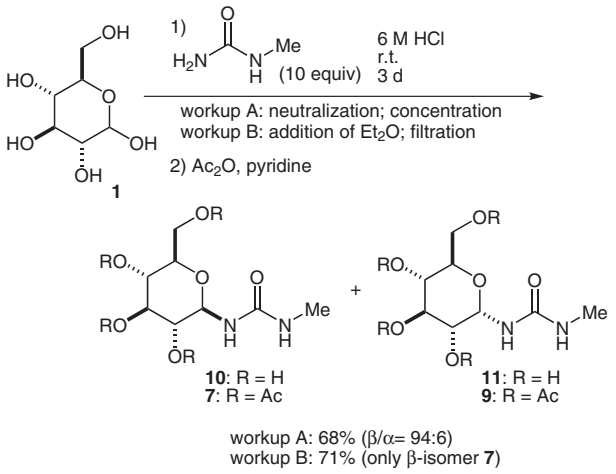
Scheme 2 Classical synthesis of d-glucose-monomethylureid by Helferich

Our initial efforts focused on identifying the structure of d-glucose-monomethylureid reported by Helferich. Accordingly, we synthesized an anomeric pair of 1-methyl-3-glucosylureas by employing a method we developed previously (Scheme 3). β-Glucosyl isonitrile **5**, prepared from acetyl glucoside **4** in four steps, was oxidized with pyridine *N*-oxide and a catalytic amount of iodine in the presence of MS 3A (anhydrous conditions) to generate the glucosyl isocyanate **6**.[2] Successive treatment of **6** with methylamine provided the β-1-methyl-3-glucosylurea **7** in 88% yield. A similar transformation employing α-glucosyl isonitrile **8**, prepared from **4** in five steps, afforded α-1-methyl-3-glucosylurea **9** in 74% yield. With these two authentic samples in hand, we carried out the experiments of Helferich. After acetylation of d-glucose-monomethylureid we found the product is identical to **7**, synthesized from β-glucosyl isonitrile **5**.

SYNLETT 2011, No. 10, pp 1462–1466
Advanced online publication: 26.05.2011
DOI: 10.1055/s-0030-1260587; Art ID: U02511ST

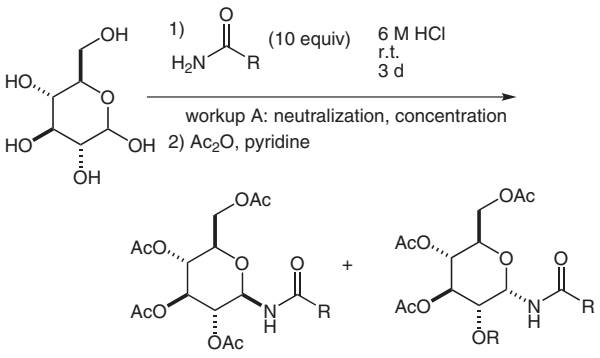


Scheme 3 Synthesis of β- and α-1-methyl-3-glucosylureas from glucosyl isonitriles



Scheme 4 Improved synthesis of 1-methyl-3-glucosylurea

Table 1 Urea Glucosylation in 6 M HCl



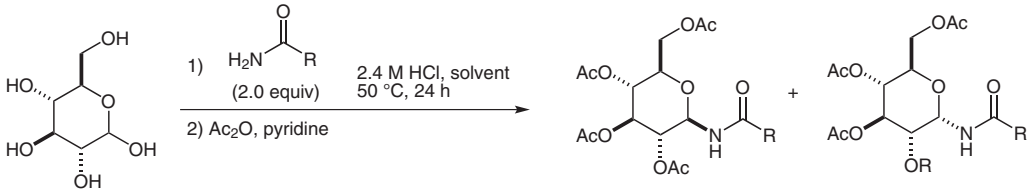
Entry[a]	Urea glucoside (R)	Yield (%)	α/β
1	**12**	67	93:7
2	**13**	56	93:7
3	**14**	26	92:8
4	**15**	24	>98:2
5	**16**	10	97:3
6	**17**	6	97:3

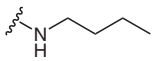
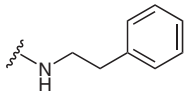
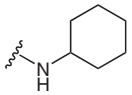
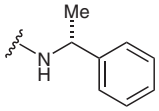
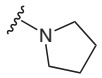
[a] The reaction was carried out on 300-mg scale of D-glucose.

We next examined conditions varying amounts of 1-methylurea, acid catalysts (HCl, H_2SO_4, acidic resins), temperature and time in order to optimize yields. This effort led to the observation that the use of excess 1-methylurea resulted in a considerable improvement in the yields of the reactions (Scheme 4). Stirring a solution of D-glucose and 1-methylurea (10 equiv) in aqueous 6 M HCl at room temperature for three days, followed by neutralization with sodium bicarbonate and concentration (workup A) afforded a solid, which was acetylated utilizing standard conditions (Ac_2O, pyridine). After chromatographic purification, a mixture of acetyl β-1-methyl-3-glucosylurea and acetyl α-1-methyl-3-glucosylurea (**7** and **9**) was obtained in 68% yield (β/α = 95:5). Although separation of this anomeric mixture was quite difficult, addition of diethyl ether after the reaction (workup B) resulted in efficient crystallization of the β-anomer **10** to result in the isolation of acetyl-β-1-methyl-3-glucosylurea **7** in 71% yield after acetylation. Because the urea group displays only a small anomeric effect, the product distribution dominating the formation of β-anomer **10** over α-isomer **11** seems to reflect the sterically driven preference for the bulky urea substituent at the pyranose anomeric position to occupy the equatorial disposition under thermodynamically controlled conditons.[9]

A range of substituted ureas was found to participate in the protective-group-free urea glucosylation using similar conditions described in Scheme 4 (Table 1). For example, simple *n*-butylurea and β-phenethylurea reacted to give products in moderate yields (entries 1 and 2; 67% and 56%, respectively). Branching at the α-position of amine moiety in the urea [entries 3 and 4; cyclohexylamine and (*R*)-α-methylbenzylamine] reduced the yield considerably (26% and 24%). Ureas derived from secondary amines (entries 5 and 6; pyrrolidine and dimethylamine) gave the

Table 2 Improved Urea Glucosylation



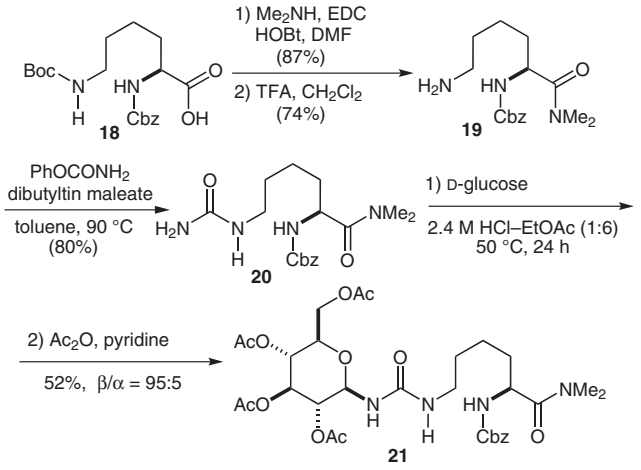
Entry[a]	Urea glucoside (R)	2.4 M HCl–solvent (ratio)	Yield[b] (%)	α/β
1	 **12**	2.4 M HCl–MeCN (1:4)	68 (75)	92:8
2	 **13**	2.4 M HCl–MeCN (1:6)	63 (70)	90:10
3	 **14**	2.4 M HCl–EtOAc (1:6)	68 (77)	>98:2
4	 **15**	2.4 M HCl–MeCN (1:6)	69 (72)	>98:2
5	 **16**	2.4 M HCl–EtOAc (1:6) 2.4 M HCl–EtOAc (1:1)	27 (29) 40[c] (42)	97:3 95:5
6	 **17**	2.4 M HCl–EtOAc (1:2) 2.4 M HCl–EtOAc (1:1)	30 (38) 49[c] (50)	97:3 93:7

[a] The reaction was carried out on 300-mg scale of D-glucose.
[b] Yields in parentheses are calculated based on the consumed amount of ureas.
[c] Yields obtained employing 10 equiv of ureas.

urea glucosides albeit in low yields (10% and 6%). Although the yields of these reactions are unsatisfactory, the facts that urea glucosides are generated in a single step from unprotected D-glucose (compare with the examples in Scheme 3) and that the process is carried out in water are noteworthy.

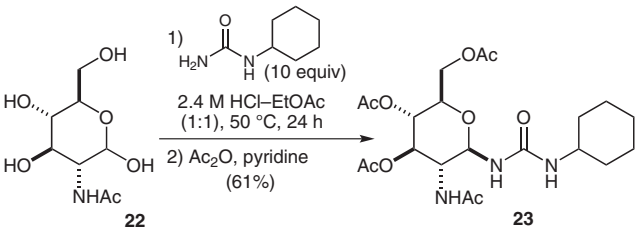
In order to increase the yields and reduce the amounts of ureas, several variations in the concentration of HCl, co-solvent and reaction temperature were explored. Considerable experimentation led to the finding that by employing 2.4 M HCl with co-solvents, such as ethyl acetate or acetonitrile, and two equivalents of ureas promote reactions that generate the corresponding urea glucosides in much higher yields[10] (Table 2). In the case of *n*-butylurea and phenethylurea (entries 1 and 2; 68% and 63%), two equivalents of urea were enough to obtain the comparable yields in Table 1, where ten equivalents of urea were employed. Glucosylation of cyclohexylurea and (*R*)-α-methylbenzylurea, using the improved conditions, afforded the products in acceptable yields (entries 3 and 4; 68% and 69%). Although yields in the case of ureas derived from secondary amines were still low (entries 5 and 6, 27% and 27%), loading increased amounts of ureas (10 equiv) led to modest levels of efficiency (40% and 49%).

With a good method for the synthesis of urea glycosides starting with unprotected carbohydrates in hand, we next focused our attention on the preparation of urea-tethered amino acid–carbohydrate conjugates (Scheme 5). Condensation of the lysine derivative **18** with dimethylamine using EDC in the presence of HOBt followed by removal of the *N*-Boc group with TFA gave the amine **19**. Transcarbamoylation of phenyl carbamate with **19** in the presence of tin catalyst furnished urea **20**.[11] Conjugation of urea **20** with D-glucose in a mixture of 2.4 M HCl–EtOAc (1:6) followed by acetylation furnished the amino acid–glucose conjugate **21** in 52% yield with a high β-selectivity (β/α = 95:5).



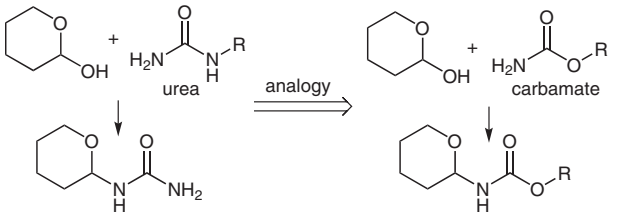
Scheme 5 Synthesis of urea-tethered amino acid–carbohydrate conjugate

We explored the possibility that the new methodology is not limited to D-glucose and can be expanded to the case of *N*-acetyl-D-glucosamine to demonstrate the potential generality of the reaction (Scheme 6). Cyclohexylurea was selected as a reactant due to the high yield and selectivity as observed in Table 2. In the event, a solution of *N*-acetyl-D-glucosamine **22** and cyclohexylurea (10 equiv) in a 1:1 mixture of 2.4 M HCl–EtOAc was stirred at 50 °C for 24 hours. After workup and acetylation of the product, the β-urea glucosamide **23** was obtained predominantly in 61% yield. The structure of **23** was unambiguously confirmed by comparison with an authentic sample prepared in six steps from **22**.[12]



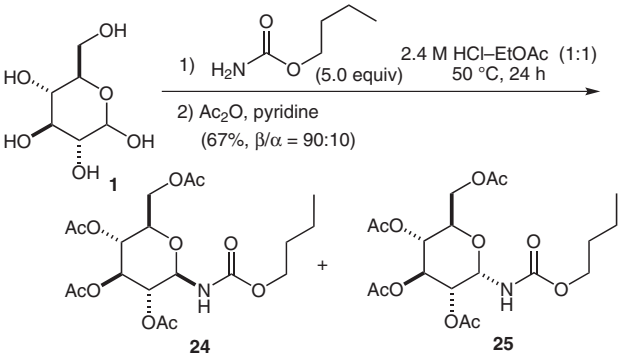
Scheme 6 Synthesis of β-urea glucosamide starting from *N*-acetyl-D-glucosamine

Finally, we attempted to extend this unique urea glycosylation procedure to the preparation of analogous glycosyl carbamate (Scheme 7), a process that, to the best of our knowledge, has not been reported previously.[13]



Scheme 7 Synthesis plan of glycosyl carbamate

Interestingly, reaction of D-glucose with five equivalents of commercially available *n*-butyl carbamate under the similar conditions as in Table 2 (Scheme 8) proceeded smoothly to furnish a mixture of glucosyl carbamates **24** and **25** in 67% yield (β/α = 90:10). Further studies of this novel carbamate glycosylation reaction are under way.



Scheme 8 Synthesis of glucosyl carbamates

The studies described above have led to the development of a new synthetic method for the preparation of urea and carbamate glycosides. The most noteworthy features are the short-step synthesis of urea and carbamate glycosides in aqueous media starting from unprotected carbohydrates.

Acknowledgment

Financial support from the Kochi University President's Discretionary Grant is greatly appreciated. Chiharu Hidaka is acknowledged for her contributions to a part of experimental work in carbamate glycosylation.

References and Notes

(1) (a) Davis, B. G. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3215. (b) Gamblin, D. P.; Scanlan, E. M.; Davis, B. G. *Chem. Rev.* **2009**, *109*, 131.

(2) (a) Ichikawa, Y.; Nishiyama, T.; Isobe, M. *Synlett* **2000**, 1256. (b) Ichikawa, Y.; Nishiyama, T.; Isobe, M. *J. Org. Chem.* **2001**, *66*, 4200. (c) Nishiyama, T.; Ichikawa, Y.; Isobe, M. *Synlett* **2003**, 47. (d) Ichikawa, Y.; Matsukawa, Y.; Nishiyama, T.; Isobe, M. *Eur. J. Org. Chem.* **2004**, 586. (e) Ichikawa, Y.; Nishiyama, T.; Isobe, M. *Tetrahedron* **2004**, *60*, 2621. (f) Ichikawa, Y.; Ohara, F.; Kotsuki, H.; Nakano, K. *Org. Lett.* **2006**, *8*, 5009.

(3) (a) Dobashi, K.; Nagaoka, K.; Watanabe, Y.; Nishida, M.; Hamada, M.; Takeuchi, T.; Umezawa, H. *J. Antibiot.* **1985**, 1166. (b) Ellestad, G. A.; Cosulich, D. B.; Broschard, R. W.; Martin, J. H.; Kunstmann, M. P.; Morton, G. O.; Lancaster, J. E.; Fulmor, W.; Lovell, F. M. *J. Am. Chem. Soc.* **1978**, *100*, 2515. For synthetic works, see: (c) Nishiyama, T.; Isobe, M.; Ichikawa, Y. *Angew. Chem. Int. Ed.* **2005**, *44*, 4372. (d) Nishiyama, T.; Kusumoto, Y.; Okumura, K.; Hara, K.; Kusaba, S.; Hirata, K.; Kamiya, Y.; Isobe, M.; Nakano, K.; Ichikawa, Y. *Chem. Eur. J.* **2010**, *16*, 600.

(4) (a) Ichikawa, Y.; Matsukawa, Y.; Isobe, M. *Synlett* **2004**, 1019. (b) Ichikawa, Y.; Matsukawa, Y.; Isobe, M. *J. Am. Chem. Soc.* **2006**, *128*, 3934. (c) Ichikawa, Y.; Matsukawa, Y.; Tamura, M.; Ohara, F.; Isobe, M.; Kotsuki, H. *Chem. Asian J.* **2006**, *1*, 717.

(5) (a) Fisher, E. *Ber.* **1914**, *47*, 1377. (b) Bannister, B. *J. Antibiot.* **1972**, 377. (c) Pinter, I.; Kovacs, J.; Toth, G. *Carbohydr. Res.* **1995**, *273*, 99. (d) Bottcher, C.; Burger, K. *Tetrahedron Lett.* **2003**, *44*, 4223. (e) Prosperi, D.; Ronchi, S.; Lay, L.; Rencurosi, A.; Russo, G. *Eur. J. Org. Chem.* **2004**, 395. (f) Prosperi, D.; Ronchi, S.; Panza, L.; Rencurosi, A.; Russo, G. *Synlett* **2004**, 1529. (g) Bianchi, A.; Ferrario, D.; Bernardi, A. *Carbohydr. Res.* **2006**, *341*, 1438. (h) Sawada, D.; Sasayama, S.; Takahashi, H.; Ikegami, S. *Tetrahedron Lett.* **2006**, *47*, 7219. (i) Yang, J.; Mercer, G. J.; Nguyen, H. M. *Org. Lett.* **2007**, *9*, 4231. (j) Sawada, D.; Sasayama, S.; Takahashi, H.; Ikegami, S. *Tetrahedron* **2008**, *64*, 8780. (k) Mercer, G. J.; Yang, J.; McKay, M. J.; Nguyen, H. M. *J. Am. Chem. Soc.* **2008**, *130*, 11210. (l) For a review, see: Spanu, P.; Ulgheri, F. *Curr. Org. Chem.* **2008**, *12*, 1071.

(6) (a) Schoorl, M. N. *Recl. Trav. Chim. Pays-Bas* **1903**, *22*, 31. (b) Benn, M. H.; Jones, A. S. *J. Chem. Soc.* **1960**, 3837.

(7) Helferich, B.; Kosche, W. *Ber.* **1926**, *59*, 69.

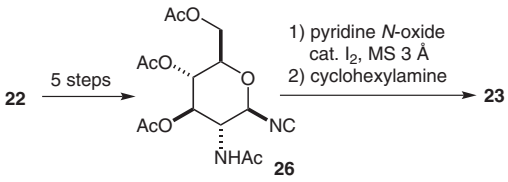
(8) Ercikson, J. G.; Keps, J. S. *J. Am. Chem. Soc.* **1953**, *75*, 4339.

(9) Ichikawa, Y.; Watanabe, H.; Kotsuki, H.; Nakano, K. *Eur. J. Org. Chem.* **2010**, 6331.

(10) A solution of D-glucose (300 mg, 1.67 mmol) and 1-*n*-butylurea (387 mg, 3.33 mmol) in a mixture of 2.4 M HCl (0.25 mL) and MeCN (1.0 mL) was stirred at 50 °C for 24 h. The mixture was neutralized by the addition of $NaHCO_3$ and washed with CH_2Cl_2 to remove excess 1-*n*-butylurea. The resulting aqueous layer was extracted with *n*-butanol. The combined *n*-butanol extracts were concentrated under reduced pressure to afford the crude 1-*n*-butyl-3-glucosylurea, which was treated with a mixture of acetic anhydride (5.0 mL) and pyridine (10 mL) at 50 °C for 3 h. After standard workup followed by chromatographic purification, a mixture of acetyl β-1-*n*-butyl-3-glucosylurea and acetyl α-1-*n*-butyl-3-glucosylurea **12** (507 mg, β/α = 92:8) was obtained in 68% yield. Concentration of CH_2Cl_2 extracts and purification by chromatography provided the recovered 1-*n*-butylurea (210 mg). The yield of 1-*n*-butyl-3-glucosylureas **12** based on the consumed 1-*n*-butylurea was calculated to be 75%.

(11) Ichikawa, Y.; Morishita, Y.; Kusaba, S.; Sakiyama, N.; Matsuda, Y.; Nakano, K.; Kotsuki, H. *Synlett* **2010**, 1815.

(12) Urea glucosamide **23** was reported to be synthesized from isonitrile **26** prepared from *N*-acetyl-D-glucosamine **22** in five steps (Scheme 9). See reference 2f.



Scheme 9

(13) These types of *N*-glycosyl carbamates were synthesized by the reaction of glycosyl isocyanates with alcohols. Authentic samples of **24** and **25** were prepared by the reaction of *n*-butyl alcohol with glucosyl isocyanates, generated from glucosyl isonitriles **5** and **8**. See reference 2d.