Convenient Stereoselective Synthesis of Substituted Ureido Glycosides Using Stable 4-Chlorophenylcarbamates without the Requirement of Lewis Acids

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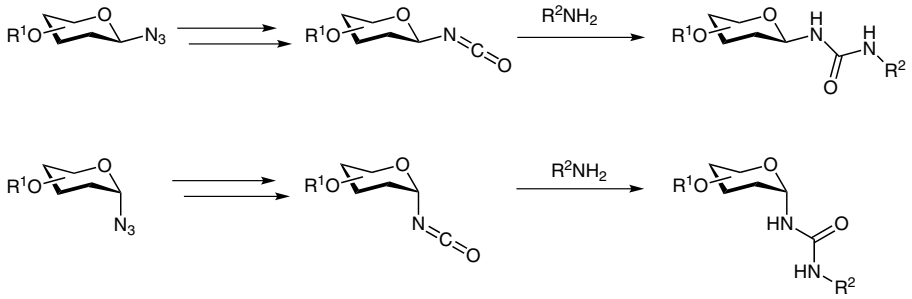
Abstract: A modification of the synthesis of substituted ureido glycosides in a stereospecific fashion is described, in which commercially available azido glycosides are reduced to the amines, which are then reacted with 4-chlorophenyl chloroformate to the corresponding 4-chlorophenyl carbamate of the glycosides. These synthetic intermediates are stable at room temperature and have a long shelf life, and can transiently form the 1-isocyanato glycosides under mildly basic conditions, which subsequently can react with amines to form substituted ureido glycosides

Key words: carbohydrates, stereoselective synthesis, azides, urea, carbamates

Carbohydrates can be tethered in various ways to other (bio)molecules, mostly via glycoside bonds. In glycoproteins common glycosidic linkages include those to threonine and serine residues. Recently, thioglycosidic linkages to cysteine residues were found in nature,[1] although with the exception of glucosinolates,[2] most thioglycosides are synthetically produced.[3] The last important type comprises the glycoside–carboxamide linkage, as found in asparagine and glutamine glycoconjugates. Conjugates of carbohydrates to (substituted) urea moieties, which are chemically similar to those of the carboxamide linkages, are a characteristic of a natural class of antibiotics; the glycocinnamoylspermidines,[4] and have recently received increasing attention as potential urea-based inhibitors of many enzymes were found.[5] Additionally, the formation of an α-ureido glycoside was a key step in the synthesis of trehazolin, a trehalase inhibitor.[6]

Although several methods for generating these urea conjugates have been described in the literature most of the older literature deals with anomeric mixtures or contain the more stable β-type urea glycosidic linkage.[7] It was only recently that synthetic procedures have appeared that exert full control over the stereochemistry of the anomeric center in ureido glycosides.[8] Currently, a number of strategies are available for selective formation of α-ureido glycosides.[5] Many of these methods rely on the condensation of an isocyanato glycoside with an amine or condensation of an amino glycoside with an isocyanate. The inherent reactivity of isocyanato glycosides, however, poses a challenge for the preparation and isolation of these compounds. Moreover, although the isolation of amino glycosides is feasible for the β-amino glycosides, the α-amino glycosides rapidly interconvert to the more stable β-isomer and cannot be stored for a prolonged period of time.[8] This can be circumvented to some extent by formation of the amino glycoside from the azido glycoside followed by direct conversion by a suitable reagent. Many currently used synthetic strategies employ a crystalline and stable azido glycoside as a masked amino glycoside. This can then be transformed into its corresponding isocyanate and subsequently into the ureido glycoside (Scheme 1).

The tetraacetyl azido glycosides themselves are easily synthesized as either the α- or the β-anomer from the corresponding 1,2-*trans*-peracetyl sugars[9–12] and are also commercially available. To circumvent the handling of phosgene derivatives leading to the isocyanato glyco-



Scheme 1 Common synthesis route in the synthesis of ureido glycosides via isocyanate intermediates

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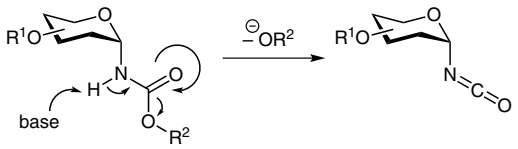
sides, much effort has been put into producing a masked version of these glycosides. Especially Ichikawa and coworkers have described two attractive strategies that produce stable masked isocyanates with a long shelf life, such as glycoside isocyanides[13] and carbamates[14] (Scheme 2), which are crystalline and easy to purify.



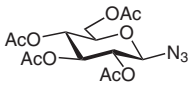
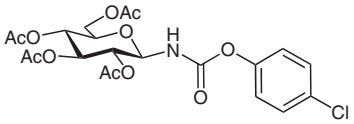
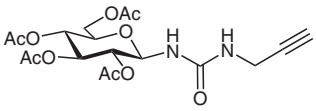
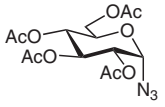
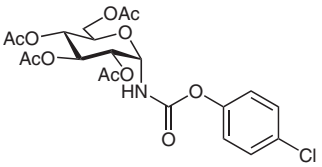
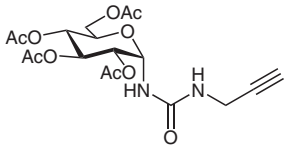
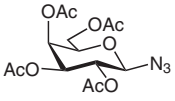
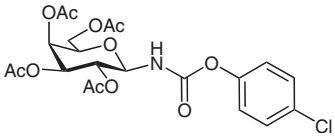
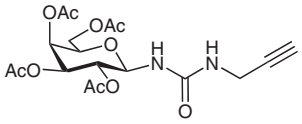
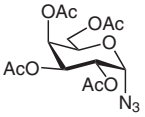
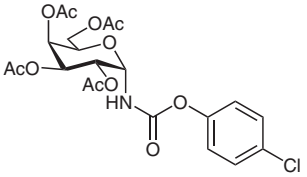
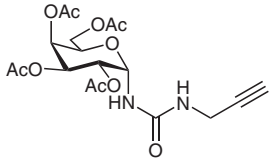
R^2	pK_a HOR^2
Me	15.5
CH_2CCl_3	12.0
Ph	10.0
4-$O_2NC_6H_4$	7.2

Scheme 2 Base-mediated elimination of sugar carbamates,[17] here depicted for an α-glycoside

In our work on glycopeptides we required an efficient synthesis of substituted ureido α-galactosides, and the strategy of Ichikawa et al. using an amine and a phenylcarbamido glycoside seemed very promising.[14] Indeed, under the conditions described, the phenyl carbamate of tetraacetyl α-amino galactoside was easily synthesized and it proved easy to crystallize the intermediate to high purity. The elimination of the phenyl carbamate, however, required refluxing with silyl chlorides under basic conditions to form the isocyanate intermediate. While successful, we surmised the possibility of performing the reaction under milder conditions. Indeed, the synthesis of the 4-nitrophenyl carbamate,[15,14] amongst other carbamates,[16] has been described in literature. The pK_a of the nitrophenol is 3 units lower than the pK_a of phenol itself (Scheme 2), thus a far greater reactivity was observed in the base-mediated elimination, to such an extent that the compounds decomposed even without a strong base present. As a result, the 4-nitrophenyl carbamate was not stable to chromatography conditions nor suitable for storage at room temperature.

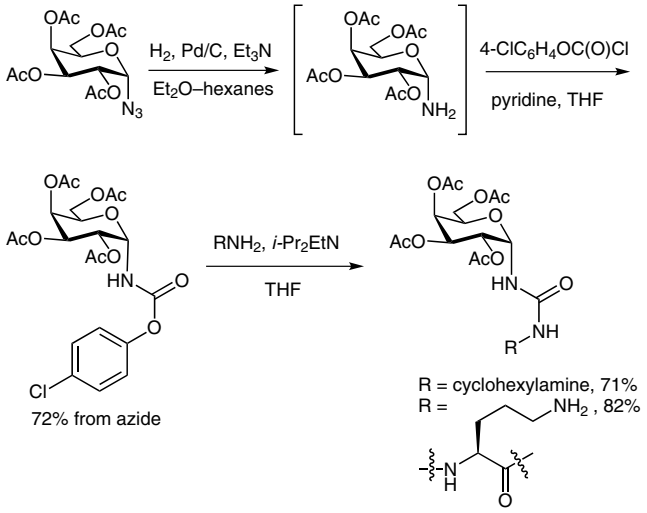
Thus, we turned our attention to carbamates containing a leaving group with a character between that of phenol and 4-nitrophenol. We turned to 4-chlorophenol with a pK_a of around 9 and investigated the corresponding 4-chlorophenyl carbamate in its ability to function as a stable precursor of an isocyanate using milder conditions than silyl chlorides in the presence of base at reflux.[14] The synthesis of the carbamate was analogous to those described earlier by Ichikawa et al.[15] The resulting chlorophenyl carbamate

Table 1 Synthesis of 4-Chlorophenylcarbamates **5**–**8** and Ureas **9**–**12**

Entry	Starting azide	4-Chlorophenylcarbamate	Yield (%)[a]	Urea	Yield (%)
1	 **1**	 **5**	68	 **9**	67[d]
2	 **2**	 **6**	69[b]	 **10**	68
3	 **3**	 **7**	60	 **11**	89[d]
4	 **4**	 **8**	72[c]	 **12**	81

[a] Isolated yield after crystallization.
[b] A small amount (<5%) of the β-anomer was present after the first crystallization.
[c] This compound was obtained as crystals co-crystallized with ca. 1 equiv of Et_2O.
[d] DBU was used as a base instead of DIPEA in the synthesis.

was then reacted with a set of primary amines at room temperature in THF in the presence of *i*-Pr_2EtN (DIPEA; Scheme 3). To our delight, the tested amines (cyclohexylamine as well as a small peptide with a free ornithine side chain) reacted cleanly with the carbamate in a few hours.



Scheme 3 Synthesis of 4-chlorophenylcarmabido α-galactoside

To establish the general applicability of this new carbamate synthon, we synthesized a small series of propargylureido glycosides (Table 1). Both anomeric forms of tetraacetyl-glucose and -galactose were synthesized, two of the most commonly used carbohydrates in carbohydrate chemistry.

As expected, the α-gluco-derived carbamate **6** reacted cleanly, under identical conditions as described for the α-galacto derivative **8**, to give **10**. The β-glucoside carbamates **5** and **7**, however, reacted very sluggish under these conditions and completion of the reaction was not achieved. Addition of the stronger neutral base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) caused the reaction to proceed to completion within an hour. The thus obtained ureido glycosides were found to be stable to these basic conditions, that is, they did not anomerize. They did need to be kept dry to prevent acetyl deprotection. However, we noticed that exposure to strong acids such as trifluoroacetic acid causes appreciable anomerization, especially of the α-urea glycosides.

The stability of the chlorophenyl carbamate **8** was checked after 15 months of storage at room temperature. No decomposition was observed by TLC, and complete retention of the stereochemistry was observed by NMR spectroscopy, in contrast to what is described about the nitrophenyl carbamate analogue, which decomposed even when stored cold.[14]

The reactivity of the 4-chlorophenyl carbamate synthon in the presence of amines at room temperature, paired with its high stability in the absence of base, suggests it might be one of the more stable reactive masked isocyanates, and its use greatly facilitates the synthesis of ureido tethered glycopeptides and derivatives.

General Procedure for the Synthesis of 4-Chlorophenylcarbamates of Glucose and Galactose

A solution of azidotetraacetyl glycosides **1**–**4** (500 mg, 1.3 mmol) and Et_3N (90 μL, 0.6 mmol) in Et_2O (30 mL) was added to a suspension of Pd/C (10% Pd on matrix activated carbon support, Sigma Aldrich, 175 mg) in *n*-hexane (25 mL). The reaction mixture was placed under a hydrogen atmosphere (3 bar, Parr apparatus) and shaken for 45 min. The reaction mixture was then diluted with THF (50 mL) and filtered over Celite. To the resulting filtrate pyridine was added (0.5 mL, 6.5 mmol), followed by 4-chlorophenyl chloroformate (370 μL, 2.6 mmol). After stirring for 45 min, the reaction mixture was diluted with EtOAc and washed with $KHSO_4$ (aq 1 M) twice and subsequently dried over Na_2SO_4. The crude products were purified over a plug of silica (2:1 hexanes–EtOAc) and recrystallized from Et_2O–hexanes to yield the 4-chlorophenylcarbamates as white microcrystalline solids. R_f = 0.32 (EtOAc–hexanes = 1:1, v/v) for all four compounds.

Compound **5**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.31 (d, *J* = 8.8 Hz, 2 H), 7.06 (d, *J* = 8.8 Hz, 2 H), 5.96 (d, *J* = 9.1 Hz, 1 H), 5.32 (t, *J* = 9.3 Hz, 1 H), 5.15–4.92 (m, 3 H), 4.33 (m, 1 H), 4.11 (m, 1 H), 3.83 (m, 1 H), 2.10 (s, 3 H), 2.09 (s, 3 H), 2.03 (s, 3 H), 2.03 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.85, 170.61, 169.89, 169.52, 153.41, 148.87, 131.14, 129.39, 122.68, 80.86, 73.37, 72.64, 70.26, 67.98, 61.53, 20.73, 20.70, 20.57 (2 C) ppm.

Compound **6**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32 (d, *J* = 8.8 Hz, 2 H), 7.10 (d, *J* = 8.8 Hz, 1 H), 6.12 (d, *J* = 7.3 Hz, 1 H), 5.75 (m, 1 H), 5.37 (m, 1 H), 5.19 (m, 1 H), 5.09 (m, 1 H), 4.33 (m, 1 H), 4.08 (m, 2 H), 2.09 (s, 3 H), 2.08 (s, 3 H), 2.06 (s, 3 H), 2.04 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.70, 170.41, 169.36, 169.13, 153.27, 148.86, 131.23, 129.46, 122.65, 76.70, 69.89, 68.48, 68.08, 68.00, 61.67, 20.71, 20.61, 20.59, 20.57 ppm.

Compound **7**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32 (d, *J* = 8.8 Hz, 2 H), 7.07 (d, *J* = 8.8 Hz, 2 H), 5.95 (d, *J* = 9.4 Hz, 1 H), 5.45 (s, 1 H), 5.21–5.10 (m, 2 H), 5.04 (m, 1 H), 4.15 (m, 2 H), 4.05 (m, 1 H), 2.16 (s, 3 H), 2.11 (s, 3 H), 2.04 (s, 3 H), 2.00 (s, 3 H) ppm.^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.11, 170.37, 170.02, 169.78, 153.39, 148.93, 131.12, 129.38, 122.70, 81.17, 72.28, 70.78, 68.02, 67.06, 61.10, 20.77, 20.66, 20.60, 20.52 ppm.

Compound **8**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33 (d, *J* = 8.8 Hz, 2 H), 7.10 (d, *J* = 8.8 Hz, 2 H), 6.19 (d, *J* = 7.5 Hz, 1 H), 5.80 (m, 1 H), 5.46–5.36 (m, 2 H), 5.28 (m, 1 H), 4.25 (m, 1 H), 4.14 (m, 2 H), 2.16 (s, 3 H), 2.10 (s, 3 H), 2.04 (s, 3 H), 2.03 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.84, 170.56, 170.21, 169.44, 153.65, 148.96, 131.13, 129.41, 122.73, 77.11, 67.47 (2 C), 67.14, 66.08, 61.60, 20.64 (2 C), 20.62, 20.58 ppm.

General Procedure for the Synthesis of *N*′-Alkyl Ureido Glycosides of Glucose and Galactose

Tetraacetyl-4-chlorophenyl carbamido glycoside **5**–**8** (100 mg, 0.2 mmol) was dissolved in THF (10 mL). Propargyl amine (25 μL, 0.4 mmol) was added, followed by *i*-Pr_2EtN (DIPEA, 100 μL, 0.5 mmol, 2.5 equiv) and in case of the less reactive β-glycosides, DBU (75 μL 0.5 mmol) was added instead of DIPEA. The reaction mixture was stirred for 1–3 h, based on completion as assayed by TLC, after which it was diluted with EtOAc, washed twice with $KHSO_4$ (1 M), and dried over Na_2SO_4. The urea products **9**–**12** were purified by column chromatography (EtOAc–hexanes = 3:2, v/v) and were obtained as white crystalline solids; R_f = ca. 0.30 (EtOAc–hexanes = 2:1, v/v) for all four compounds.

Compound **9**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.90 (d, *J* = 9.5 Hz, 1 H), 5.63 (t, *J* = 5.3 Hz, 1 H), 5.27 (m, 1 H), 5.12 (m, 1 H), 5.02 (m, 1 H), 4.87 (t, *J* = 9.5 Hz, 1 H), 4.24 (m, 1 H), 4.02 (m, 1 H), 3.90 (m, 2 H), 3.80 (m, 1 H), 2.24 (t, *J* = 2.4 Hz, 1 H), 2.02 (s, 3 H), 2.00 (s, 3 H), 1.97 (s, 3 H), 1.95 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.98, 170.79, 169.96, 169.73, 156.32, 80.25, 79.95, 73.10, 72.99, 71.61, 70.48, 68.30, 61.89, 29.88, 20.75, 20.74, 20.58, 20.56 ppm.

Compound **10**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.11 (d, *J* = 4.4 Hz, 1 H), 5.78 (t, *J* = 5.2 Hz, 1 H), 5.56 (t, *J* = 5.1 Hz, 1 H), 5.40 (t, *J* = 9.8 Hz, 1 H), 5.14–4.95 (m, 2 H), 4.26 (m, 1 H), 4.14–3.96 (m, 4 H), 2.26 (t, *J* = 2.3 Hz, 1 H), 2.07 (s, 3 H), 2.03 (s, 3 H), 2.01 (s, 3 H), 2.00 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.66, 170.24, 169.43, 169.24, 157.20, 80.11, 76.77, 71.63, 69.91, 68.83, 68.27, 67.20, 61.82, 29.96, 20.71, 20.58, 20.55 (2 C) ppm.

Compound **11**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.65 (d, *J* = 8.8 Hz, 1 H), 5.44 (d, *J* = 1.4 Hz, 1 H), 5.26–5.00 (m, 4 H), 4.13 (m, 2 H), 4.09–3.84 (m, 3 H), 2.24 (t, *J* = 2.4 Hz, 1 H), 2.15 (s, 3 H), 2.06 (s, 3 H), 2.05 (s, 3 H), 1.99 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.25, 170.59, 170.16, 169.79, 156.07, 80.43, 80.12, 72.23, 71.53, 71.08, 68.23, 67.35, 61.46, 29.93, 20.84, 20.75, 20.58, 20.51 ppm.

Compound **12**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.12 (d, *J* = 4.1 Hz, 1 H), 5.76 (t, *J* = 5.3 Hz, 1 H), 5.60 (s, 1 H), 5.40 (s, 1 H), 5.30 (m, 2 H), 4.28 (m, 1 H), 4.20–4.04 (m, 2 H), 4.00 (m, 2 H), 2.24 (t, *J* = 2.4 Hz, 1 H), 2.14 (s, 3 H), 2.06 (s, 3 H), 2.05 (s, 3 H), 1.98 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.47, 170.20, 170.12, 169.61, 157.59, 80.15, 77.34, 71.50, 67.73, 67.27, 66.44, 66.19, 61.96, 29.94, 20.71, 20.67, 20.60, 20.55 ppm.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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