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Stereoselective Synthesis of Glycosyl Carbamates as New Surfactants and Glycosyl Donors.

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Abstract : O-acyl-protected glycosyl *N*-alkyl and *N*-phenyl carbamates are obtained with 100% diastereoselectivity from anomerically unprotected mono or disacacharides. Long-chain alkyl carbamates are surfactants. *N*-phenyl carbamates are good glycosyl donors. © 1997 Elsevier Science Ltd.

Alkyl glycosides possessing one hydrophilic sugar residue and one lipophilic long alkyl chain linked by a O-glycosidic bond have been gained wide interest as non-ionic surfactants and have become commercially available. Plusquellec reported another type of non-ionic glycosidic surfactant in which the lipophilic tail is positioned on C-6 hydroxyl group of methyl glycosides *via* a carbamate bond. [1] So, in the course of our research dealing with new glycosidic surfactants, we speculate that glycosyl carbamates could be very attractive candidates.

Despite the copious literature on the addition reaction of alcohols to isocyanates leading to carbamates, only few examples concerning the addition reaction of the anomeric hydroxyl group of glycopyranoses to isocyanates are described. Unprotected lactose reacted with long-chain alkyl isocyanates to give 1-β-O-lactosyl in low yield (24-40%)[2]. Reaction of methylated glucose with phenyl isocyanates afforded the corresponding carbamates with moderate or low stereoselectivity[3]. More recently Kunz and his colleague obtained *N*-allyl glycosyl carbamates in high yield and good β-diastereoselectivity[4]. Finally Sheeren reports the synthesis of

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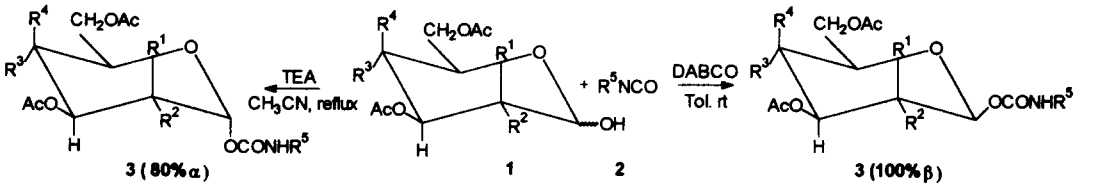
β-glucuronyl carbamate prodrugs with complete diastereoselectivity[5].

In this paper, we wish to report the 100% β– or high α–diastereoselective preparation of various glycosyl carbamates, some of them showing tensioactive properties. We also describe a new glycosylation reaction with *N*-phenyl glycosyl carbamates as glycosyl donors.

Synthesis of the glycosyl carbamates. (Scheme1)

The synthesis of O-β-glycosyl carbamates was carried out in toluene, at room temperature with a large excess of 1,4-diazabicyclo[2.2.2]octane (DABCO). Starting from O-acetylated carbohydrates **1** having an unprotected anomeric hydroxyl group[6] and isocyanates[7] **2**, carbamates **3** were obtained in very good yield with 100% β–diastereoselectivity, except for mannose **3c** (Table 1).



Scheme 1

Table 1 : Synthesis of *N*-glycosyl carbamates **3**.

1-3	R^1	R^2	R^3	R^4	R^5	Yield %
a	H	OAc	H	OAc	C_7H_{15}	94
b	H	OAc	OAc	H	C_7H_{15}	84
c	OAc	H	OAc	H	C_7H_{15}	61[8]
d	H	OAc	β-galactosyl	H	C_7H_{15}	60
e	H	OAc	H	OAc	C_6H_5	98
f	H	OAc	OAc	H	C_6H_5	99
g	OAc	H	OAc	H	C_6H_5	97

It is of considerable importance to perform the reaction with a sterically hindered base as DABCO in order to increase the 1,3-diaxial steric effect in the α-transition state. Thus β–anomers, which are also better nucleophiles, are largely predominant, leading to complete β–diastereoselectivity. As expected, the influence of the temperature and of the solvent is very important for the selectivity of the reaction. When the addition was carried out in acetonitrile in presence of triethylamine (TEA) at reflux, the α-anomer was obtained with good diastereoselectivity (70-80%). The rate of the reaction depends on the temperature and concentration of base. The higher is the concentration, the faster is the reaction. It should be noted that the observed selectivity is not correlated with the anomeric ratio of the respective glycopyranoside hemiacetals **1** in solution.

Glycosyl carbamates as surfactants

The β-derivatives **3a, 3b** and **3c** (R^5=C_7H_{15}) were quantitatively deacetylated (MeOH/MeONa) to give deprotected glycosyl carbamates. These surface-active compounds highly reduce the superficial tension of water and exhibit very interesting solubilizing properties of nuclear, mitochondrial, and microsomial proteins similar to Triton X100 (Table 2). However, because their moderate solubility, the glycosyl carbamates do not form micelles. We note that the nature of the hydrophilic head (glucose, galactose or mannose) and the anomeric configuration do not affect significantly the properties of these amphiphiles molecules.

Glycosyl carbamates with shorter (R^5 = C_5H_{13}), longer (R^5 = C_9H_{17}) or perfluoroalkyl lipophilic tails (R^5 = $C_2H_4C_6F_{13}$) were also prepared but they did not present interesting surface-active properties.

Table 2 : Surface tension and solubilizing properties of *N* long-chain-alkyl glycosyl carbamates **3a-3c**

	Surface tension (mN/m)[a] (Concentration g/l)	Solubilization of proteins[b]		
		Nuclear	Mitochondrial	Microsomial
3a	23.60 (4.0)	62.5	75.4	72.8
3b	23.25 (3.2)	64.5	72.5	73.3
3c[c]	31.30 (2.9)	60.9	71.7	72.5
Triton X100		62.2	74.9	76.2

a) The surface tension was measured at concentration corresponding to the maximum solubility.

b) The solubilizing properties of these products were assayed on subcellular rat liver fractions according to a procedure previously reported.[9]

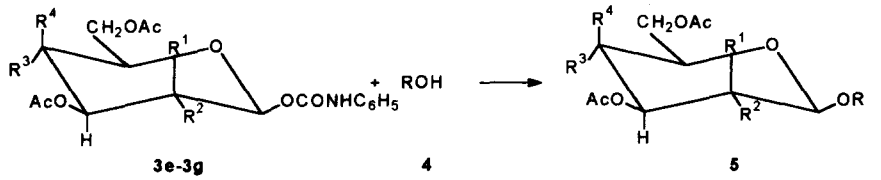
c) α-anomer

N-phenyl glycosyl carbamates as glycosyl donors.

The instability of *N*-allyloxycarbonyl group towards soft electrophiles stimulated the development of a glycosylation method which is based on the electrophilic intramolecular cyclization of anomeric *N*-allyl carbamates[4]. We wish to report another glycosylation procedure with *N*-phenyl-β-glycosyl carbamates as glycosyl donors.

The glycosylation (scheme 2) was carried out in dichloromethane, in presence of molecular sieves (4Å), at room temperature with an excess of acceptor **4** (1.5 equivalent) and $BF_3.OEt_2$ (1.5 equivalent) as promoter. The glycosides **5** were obtained in moderate or good yields after purification by flash chromatography (Table 3).

The glycosyl carbamates carrying participating group at the C-2 position react under complete stereoselectivity leading to the formation of β-glycosides. Glycosylations with non-participating benzyl protecting group afford an anomeric mixture in which the α-anomer is predominant. It should be noted that isopropylidene and benzyloxycarbonyl protecting groups remain unaffected during the course of the glycosylation.



Scheme 2

Table 3 : Glycosylation with *N*-phenyl glycosyl carbamates and BF_3.

Glycosyl donors 3	Glycosyl Acceptor 4	Yield
3e	1-Butanol	52%
3e	1-Octanol	66%
3e	Benzyl alcohol	75%
3e	N-Benzyloxycarbonyl-ethanolamine	53%
3e	1,2,3,4-Diisopropylidene-D-galactopyranose	68%
3f	Benzyl alcohol	62%
3g	Benzyl alcohol	63%
3g	N-Benzyloxycarbonyl-ethanolamine	50%

In conclusion, we report in this paper the completely β-diastereoselective and good α–diastereoselective synthesis of glycosyl carbamates. Moreover, we demonstrate the interest of long-chain alkyl carbamates as surfactants and the utility of *N*-phenyl glycosyl carbamates as glycosyl donors. Further extensions of these preliminary results are presently under investigation in our laboratory.

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