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## SYNTHETIC COMMUNICATIONS, 32(2), 181-187 (2002)

## REGIOSELECTIVE REACTION OF UNPROTECTED SUGARS WITH URETHANE N-CARBOXYANHYDRIDES FOR THE SYNTHESIS OF NEW SURFACTANTS

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## ABSTRACT

Reaction of urethane *N*-carboxyanhydrides with unprotected amino sugars was the key step in the synthesis of new trimodular surfactants.

Alkyl glycosides possessing one hydrophilic sugar residue and one lipophilic long alkyl chain linked by a glycosidic bond have become commercially available as non-ionic surfactants. These compounds are characterized by a low toxicity, high biodegradability as well as excellent skin compatibility.<sup>1</sup> More recently glycosyl amides<sup>2</sup> and glycosyl carbamates<sup>3</sup> have been reported as surfactants. They were prepared using chemical or enzymatic methods.

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Because of environmental reasons, it seems advantageous to develop surfactants from raw materials of agricultural origin such as carbohydrates, proteins; these natural compounds are optically pure and inexpensive.

We decided to develop a new family of surfactants including one hydrophilic sugar residue and one lipophilic long chain linked by an amino acid residue. In this study the fatty chain was linked to the amino function of the amino acid whereas the sugar was bound to the acid function. To create this bond, commercially available urethane *N*-carboxyanhydrides (UNCAS) appear to be good candidates; the versatile reactivity of these stable compounds has been explored<sup>4</sup> and we were interested to examine their behaviour with unprotected sugar derivatives in the first step of our synthesis.

Reaction of urethane-*N*-carboxyanhydrides was first investigated with amino sugars because the amide bond is chemically and physically very stable in alkaline media. Three amines were used: *N*-methylglucamine 1, glucosylamine 2, 2-deoxy-2-amino glucose 3 (Scheme 1).



The first experiments were carried out starting from *N*-methyl glucamine and Ala-NCA *N*-protected by different groups: *t*-butyloxy-carbonyl (Boc), benzyloxycarbonyl (Z) and fluorenylmethoxycarbonyl (Fmoc) (Scheme 2). *N*-methyl glucamine contains several hydroxyl functions that can also react with the UNCA, so it was necessary to find suitable operating conditions allowing selective *N*-acylation. While the reactions may be conducted in both DMF and CH<sub>3</sub>CN as solvent, the results obtained in DMF were generally superior; in CH<sub>3</sub>CN several compounds were obtained, the regioselectivity was very low. Influence of the protecting group, of the temperature, of the reaction time and of the stoichiometry (ratio Amine/UNCA) were studied. The results are reported in Table 1.

The nature of the protecting group had not a great influence on the yield (the Z group giving the best yields) and on the regioselectivity. However the stoichiometry is very important; with a ratio sugar/UNCA = 1 (Entries 2 and 4), a mixture of two products was obtained, a

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Scheme	2.
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Entry	UNCA	$\mathrm{T}^\circ$	Ratio Sugar/UNCA	Solvent	Time (h)	Product	Yield (%)
1	4a	r.t.	2	DMF	24	6a	36
2	"	"	1	,,	"	,,	30
3	"	"	2	CH <sub>3</sub> CN	"	8a mixture	47
4	4b	"	1	DMF	"	6b	82
						8b	
5	4b	"	2	,,	"	6b	70*
6	,,	0	,,	"	,,	,,	62*
7	"	-25	,,	,,	"	,,	47*
8	,,	-60	,,	"	8	,,	54*
9	,,	-78	,,	••	,,	**	70*
10	,,	r.t.	,,	,,	1/2	,,	61*
11	,,	,,	2	"	8	,,	68*
12	4c	,,	1	"	24	9	62**
13	,,	,,	2	"	,,	,,	42**
14	,,	,,	0.5	,,	"	6c	23*
						8c	21*
15	"	,,	0.5	"	72	6c	46*
						8c	11*

Table 1. Reaction of N-Methyl Glucamine with Urethane-Ala-NCA

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Isolated yield after column chromatography. \*Isolated yield after preparative HPLC. \*\*Yield based on <sup>1</sup>H NMR spectra.

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monosubstituted compound with an amide function (**6a**, **6b**) and a disubstituted compound containing an amide and an ester functions (**8a**, **8b**). With the same ratio and the Fmoc group as protecting group (Entries 12 and 13) the reaction afforded directly compound **9**, *N*-methyl glucamine being able to cleave the Fmoc group. With the ratio sugar/UNCA = 2 (Entries 1 and 5) a good regioselectivity was obtained and in all cases only *N*-methylglucamine amidation took place. When the temperature was lowered to  $-78^{\circ}$ C, the yield remained practically identical (Entries 6–9). The reaction time had not a great influence on the yield, the reaction seemed to be rapid. Reaction of *N*-methylglucamine with Z-Phe NCA **5b** using the same reaction conditions (ratio:sugar/UNCA = 2) afforded the *N*-acylated compound **7b** in 70% yield.

To connect the fatty chain, compounds **6** were *N*-deprotected using standard methods to give **9** and reaction with lauroyl chloride in  $H_2O/EtOH$  in the presence of Na<sub>2</sub>CO<sub>3</sub> afforded **10** in good yield (Scheme 3).



10 was weakly soluble in water, to improve the solubility the fatty chain was shortened and coupling of 9 with hexanoic acid chloride afforded 11 (soluble in water) in 57% yield.

This methodology was applied starting from glycosylamine 2 easily prepared using Lubineau's method<sup>5</sup> and 2-deoxy-2-aminoglucose 3; the regioselectivity of the reaction with 4a, 4b, 4c depends on the stoichiometry,

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*Table 2.* Reaction of Glucosylamine 2 and 2-Deoxy-2amino Glucose **3** with Urethane-Ala-NCA

Amine	UNCA	Product	Yield (%)
2	4a	12a	32
"	4b	12b	45
**	4c	12c	48
3	4a	13a	53
"	4b	13b	45
,,	4c	13c	50

the single *N*-acylation product (12 from 2 and 13 from 3) was obtained if the ratio sugar/UNCA = 2 (Table 2).

In conclusion the procedure reported herein provides a very attractive and efficient methodology. It should be applicable for the synthesis of a great variety of trimodular compounds whose physicochemical properties are under investigation.

### **EXPERIMENTAL**

<sup>1</sup>H NMR spectra were recorded on a Brucker at 200 MHz. Mass spectra were recorded on a JEOL DX 300 and SX 102. Infra red spectra were performed on a Perkin Elmer Paragon 1000. Microanalysis were performed by the Service of CNRS at Vernaison (France). Melting points are uncorrected. Analytical thin layer chromatography (TLC) was performed using Merck Silica gel 60 F254 precoated plates with a fluorescent indicator. Visualization was accomplished by nynhydrin solution. The starting UNCAS were from Isochem (Gennevilliers, France).

General Procedure for the Reaction of Aminosugars with UNCA: To the amino sugar (1, 2 or 3) (0.52 mmol) dissolved in anhydrous DMF (4 ml) under magnetic stirring was added at room temperature urethane-Ala-NCA (0.25 mmol) dissolved in DMF (2 ml), the reaction being monitored by T.L.C. The solvent was evaporated to give an oil which was purified by column chromatography on silica gel using an appropriate solvent mixture

**6a:** solvent mixture (CHCl<sub>3</sub>/EtOH/AcOH: 12/3/0.1). m.p. = 56–58°C  $[\alpha]_D = -17$  (c = 1, CH<sub>3</sub>OH). IR (KBr): 3296, 2925, 2857, 1695, 1628 cm<sup>-1</sup>. <sup>1</sup>H NMR (D<sub>2</sub>O) d 1.15 (d, 3H, J = 6.9 Hz); 1.25 (s, 9H); 3–3.2 (2s, 3H); 3.3–4 (m, 8H); 4.45 (q, 1H, J = 6.9 Hz). M.S.: M + 1 = 367 (ES).

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**6b:** solvent mixture (CHCl<sub>3</sub>/EtOH/AcOH: 80/19/1) m.p. =  $46-48^{\circ}$ C (H<sub>2</sub>O). [ $\alpha$ ]<sub>D</sub> = -37 (c = 1, H<sub>2</sub>O). IR (KBr): 3319, 1729, 1646 cm<sup>-1</sup>. <sup>1</sup>H NMR (D<sub>2</sub>O):  $\delta$  1.3 (d, 3H, J = 6.52 Hz); 2.9–3.2 (2s, 3H); 3.3–4.3 (m, 8H); 4.5 (q, 1H, J = 6.7 Hz); 5.15 (s, 2H); 7.45 (m, 5H). Anal. calcd. for C<sub>18</sub>H<sub>28</sub>O<sub>8</sub>N<sub>2</sub>, 0.5 H<sub>2</sub>O: C 52.80, H 6.89, N 6.84, found C 52.77, H 6.96, N 7.07.

**6c:** m.p. =  $62-64^{\circ}C [\alpha]_{D} = -10$  (c = 1, CHCl<sub>3</sub>). IR (KBr): 3283, 2914, 2887, 1711, 1696, 1646 cm<sup>-1</sup>. <sup>1</sup>H NMR (D<sub>2</sub>O)  $\delta$  1.3 (d, 3H, J = 6.5 Hz); 3–3.2 (2s, 3H); 3.4–4.4 (m, 11H); 4.6 (q, 1H, J = 6.5 Hz); 7.2 (m, 8H). M.S.: M + 1 = 489 (ES).

**7b:** m.p. = 48–50°C. IR (KBr): 3293, 2939, 2887, 1721, 1705, 1688 cm<sup>-1</sup>. <sup>1</sup>H NMR (D<sub>2</sub>O)  $\delta$  2.9–3.2 (2s, 3H); 3 (d, 2H, J = 6.3 Hz); 3.3–3.7 (m, 8H); 3.9 (q, 1H, J = 6.3 Hz); 5 (s, 2H); 7.2 (m, 10H). Anal. Calcd for C<sub>24</sub>H<sub>32</sub>O<sub>8</sub>N<sub>2</sub>, H<sub>2</sub>O: C 58.28, H 6.92, N 5.66, found C 58.72, H 6.74, N 5.68.

**12a:** solvent mixture (CHCl<sub>3</sub>/MeOH/NH<sub>4</sub>OH: 20/15/2) m.p. = 120– 122°C. IR (KBr): 3418, 2917, 2881, 1688, 1680 cm<sup>-1</sup>. <sup>1</sup>H NMR (D<sub>2</sub>O):  $\delta$  1.2 (d, 3H, J = 7 Hz); 1.3 (s, 9H); 3.25–3.8 (m, 6H); 3.9 (q, 1H, J = 7 Hz); 5 (d, 1H, J = 3.35 Hz).

**13a:** solvent mixture (CHCl<sub>3</sub>/EtOH/AcOH: 80/20/1) m.p. = 143–145°C. IR (KBr): 3320, 2971, 1684, 1646 cm<sup>-1</sup>. <sup>1</sup>H NMR (D<sub>2</sub>O):  $\delta$  1.45 (d, 3H, J = 6.75 Hz); 1.55 (s, 9H); 3.5–4.1 (m, 6H); 4.3 (q, 1H, J = 6.8 Hz); 5.3 (d, 1H, J = 3.3 Hz). Alanine *N*-methylglucamide **9** was obtained directly (Table 1, Entry **12**) of after cleavage of the *N*-protecting groups using standard methods.

**9** (0.22 g, 0.82 mmole) was dissolved in a solution of Na<sub>2</sub>CO<sub>3</sub> (0.11 g) in EtOH/H<sub>2</sub>O (3/1) under argon, the mixture was cooled to  $0^{\circ}$ C and lauric acid chloride or hexanoic acid chloride (4 eq) was added; the reaction took place spontaneously. **10** was obtained after precipitation using CHCl<sub>3</sub>.

Yield: 55% m.p. =  $102-104^{\circ}$ C. IR (KBr): 3330, 2907, 2849, 1659, 1647 cm<sup>-1</sup>. <sup>1</sup>H NMR (CD<sub>3</sub>OD):  $\delta$  0.8 (t, 3H, J = 6.8 Hz); 1.25 (s, 16H); 1.4 (d, 3H, J = 7.2 Hz; 1.6 (m, 2H); 2.3 (t, 2H, J = 7.1 Hz); 2.9–3.2 (2s, 3H), 3.4–4.2 (m, 8H); 4.4 (q, 1H, J = 7.2 Hz). M.S.: M + 1 = 449 (ES).

11 was obtained after elimination of the excess of fatty acid by extraction with diethylether, evaporation of the aqueous layer and crystallization from water/methanol.

Yield: 57%. IR (KBr): 3340, 2917, 2859, 1669, 1657 cm<sup>-1</sup>. <sup>1</sup>H NMR (D<sub>2</sub>O):  $\delta$  0.8 (t, 3H, J=5.8 Hz); 1.25 (m, 6H); 1.5 (m, 2H); 2.3 (t, 2H, J=5.4 Hz); 2.9–3 (2s, 3H); 3.2–3.8 (m, 8H); 4.1 (q, 1H, J=5.4 Hz). M.S.: M+1=365 (ES). Anal. Calcd. for C<sub>16</sub>H<sub>32</sub>O<sub>7</sub>N<sub>2</sub>: C 52.74, H8.79, N7.69 found C 52.69, H8.82, N7.75.

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