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Fast synthesis of uronamides by non-catalyzed opening of glucopyranurono-6,1-lactone with amines, amino acids, and aminosugars

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ABSTRACT

A series of glucuronamides have been easily prepared by reaction of glucopyranurono-6,1-lactone with a wide variety of amines. Primary and secondary amines gave the corresponding amides in short times, high yields. Diamines led to diuronamide compounds, whereas glucuronic acid conjugates were obtained with amino acids. The reaction with aminosugars afforded disaccharide analogues. In all products, the anomeric position is free for further conversion.

The formation of amide bond has a real importance in the organic synthesis because it is found in many structures like proteins, polyamides, and complex carbohydrates compounds such as meonomycin,[1] capuramycin[2], and glycyrrhizic acid conjugates.[3] Generally, the preparation of glucuronamide involves carboxylic acid activation as a chloride,[4] or by using a method derived from peptide synthesis.[5,6] To obtain glucofuranuronamide derivatives, a glucofuranurono-6,3-lactone intermediate has been used, for example, in the synthesis of bolaamphiphiles[7] or as a key-step for the preparation of glycosylated *ortho*-carboranyl amino acid or mono- and bis-glucuronylated carboranes.[8]

Previously, we have developed a one-pot synthesis of acetylated glucopyranurono-6,1-lactone from glucuronic acid (GlcA) under microwave irradiation, and this lactone was used to prepare alkyl (alkyl-D-glucopyranoside)uronate derivatives.[9]

Herein, we examined the reaction between the 6,1-lactone **1** and various amines.

Firstly, we examined the reactivity of the 6,1-lactone **1** with various aliphatic amines at room temperature (Table 1). The reaction needs only a small amount of dichloromethane as a solvent and 1.2 equiv of the amine. For primary amines, the reaction was followed by TLC and furnished quickly (ca. 5 min) the corresponding amides **3a–e** in good to excellent yields (81–96%) after purification (Table 1, entries 1–5).

All compounds were isolated as a mixture of α,β anomers and were characterized by NMR spectroscopy and ESI-MS spectrometry. Thus, for the major α products, uronamide C-6 resonances were observed at δ 168.6 (**3a** and **3b**), 168.3 (**3c**), 167.8 (**3d**), and 168.5 (**3e**). NH protons appear at δ 6.60 (**3a**) 6.59 (**3b**), 6.73 (**3c**), 6.39 (**3d**), and 6.62 (**3e**).

For secondary amines (Table 1, entries 6 and 7), piperidine reacted as quickly as primary amines in 95% yield. In the case of di-*n*-octylamine, the reaction was really slow. To increase the reaction rate, the mixture was heated at 40 °C and after 30 min the corresponding amide **3f** was obtained in 73% yield. On the other hand, the reaction with di-*n*-isopropylamine failed, in spite of several attempts using longer reaction times or heating, probably because of the hindered character of this secondary amine. C-6 resonances of disubstituted amines were observed at δ 166.0 and 165.0 for **3f**[10] and **3g**, respectively.

The reactivity with diamines was then studied. The yield of the reaction with ethylenediamine (Table 1, entry 8, 94%) was higher than 1,6-hexanediamine (Table 1, entry 9, 59%), certainly due to the lower solubility of the latter in the reaction mixture. When the reaction was conducted in DMF, the yield increased to 92% in 5 min. In both cases, the main product resulted from di-N-substitution, as shown by mass spectrometry: $[MNa]^+$ peaks appear at m/z 687.2 (**3h**, 94% yield) and 743.2 (**3i**, 59% yield) corresponding to interesting dimeric molecules.

In addition, we tested the reaction with amines containing different chemical functions. Coupling to amino acids was first assayed, as amino acids are only available in the hydrochloride form, 1 equiv of triethylamine was added in the reaction mixture.

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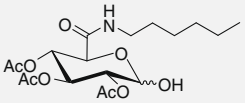
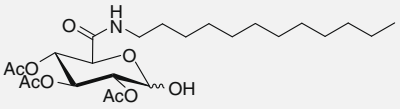
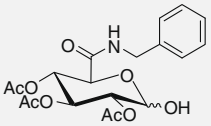
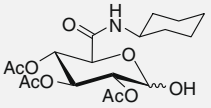
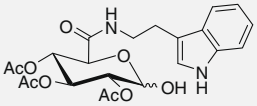
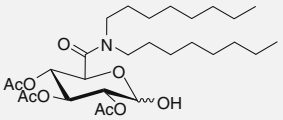
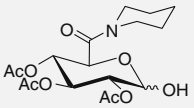
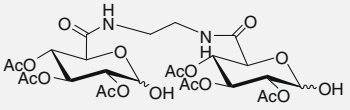
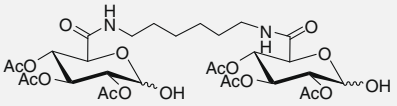
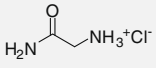
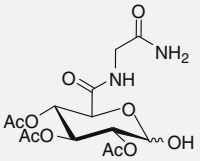
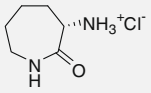
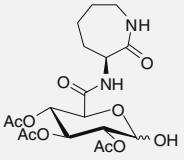
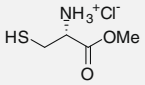
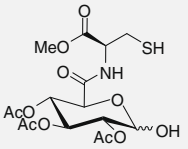
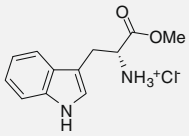
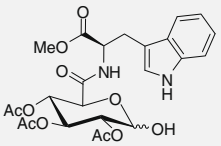
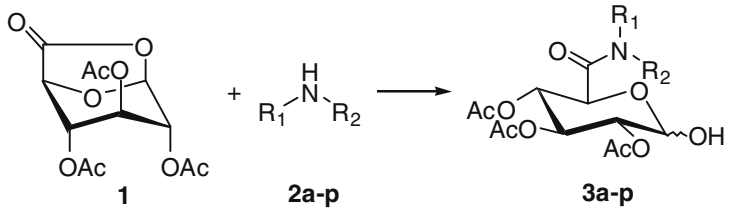
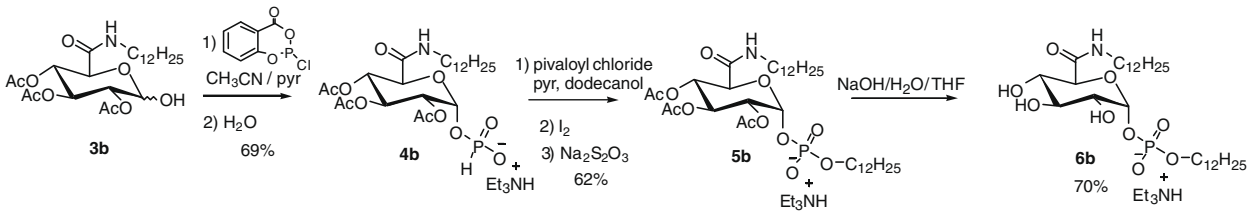
Table 1
Reactions with aliphatic amines, amino acids, caprolactam

Entry	Amine	Temperature	Time	Products		Yield
1	*n*-Hexylamine	rt	5 min		**3a**	81%
2	*n*-Dodecylamine	rt	5 min		**3b**	87%
3	Benzylamine[14]	rt	5 min		**3c**	96%
4	Cyclohexylamine	rt	5 min		**3d**	89%
5	Tryptamine	rt	10 min		**3e**	92%
6	Di-*n*-octylamine	rt 40 °C	30 min 30 min		**3f**	Traces 73%
7	Piperidine	rt	5 min		**3g**	95%
8	Ethylenediamine [c]	rt	5 min		**3h**	94%
9	1,6-Hexanediamine [c]	40°C rt	5 min 5 min		**3i**	59%[a] 92%[b]
10		rt	20 min		**3j**	88%[a]
11		rt	5 min 16 h		**3k**	29%[a] 91%[b]
12		rt	5 min		**3l**	92%
13		rt	60 min		**3m**	95%

[a] The reaction was carried out in dichloromethane and methanol (1:1 v/v) to increase the amide solubility.
[b] The reaction was performed in DMF.
[c] The reaction was carried out with 1.9 equiv of lactone **1** for 1 equiv of diamine reagent.

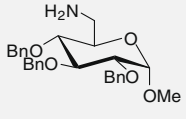
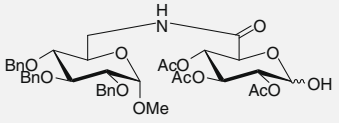
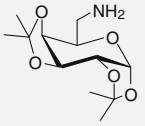
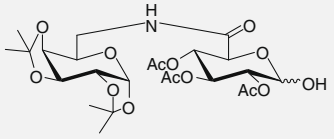
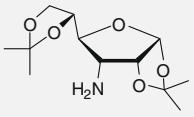
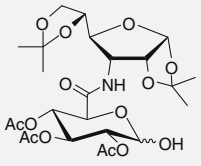


Scheme 1. Reaction between the 6,1-lactone **1** and amines **2a–p**.



Scheme 2. Phosphorylation of the anomeric position of *N*-dodecylglucuronamide **3b**.

Table 2
Reactions with amino sugars

Entry	Sugars	Temperature	Time	Products		Yield (%)
1		rt	5 min		**3n**	91
2		rt	5 min		**3o**	95
3		rt	10 min		**3p**	82

In the absence of triethylamine no amide formation was observed. As shown in Table 1 (entries 10, 12, and 13), the reaction led to the coupled products in high yields with glycine, cysteine, and tryptophan (88%, 92%, and 95%, respectively) making this approach suitable for the synthesis of glycopeptides. On the other hand, the poor yield obtained with the caprolactame derivative may be assigned to its low solubility in DCM. Accordingly, when the reaction was performed in DMF, compound **3k** was obtained in 91% yield (Table 1, footnote a).

As shown in Scheme 1, the caprolactam glucuronamide derived is formed and the anomeric position is free. The scaffold **3** can be used as a starting material for the preparation of glycosyl donors such as trichloroacetamidates[6a] or phosphates.[11] We have phosphorylated the anomeric hydroxyl using the procedure developed by van Boom and co-workers (Scheme 2).[12] The glucuronamide **3b** was treated by salicylchlorophosphite, the hydrogen phosphonate intermediate **5b** was then transformed into a mixed anhydride with pivaloyl chloride followed by a coupling with dodecanol and an oxidation with iodine in the presence of water to give the corresponding phosphate **6b**.[13]

Several research groups are interested in the preparation of amide bond containing disaccharide analogues. The current methodology is based on peptide synthesis.[15] Recently, Crich and Sasaki[16] developed a new two-step strategy based on the reaction of a thiocarboxylate with an electrondeficient isocyanate to give the corresponding amide. Our approach involves the reaction of the 6,1-lactone with an amine derived from a sugar. As shown in Table 2, the 6→6 (entries 1 and 2) or 3→6 (entry 3) disaccharide analogues were obtained in short times and in high yields (82–95%).

In conclusion, we have developed an efficient and fast reaction to prepare glucuronamides from glucopyranurono-6,1-lactone and different amine-containing compounds. Moreover, the formed products can be used as scaffolds or key intermediates for the synthesis of more complex molecules. A new phosphodiester amphiphile derived from D-glucopyranuron-*N*-dodecylamide has been prepared; other derivatives with different alkyl chains are currently synthesized.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.03.019.

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10. *Typical experimental procedure for the preparation of glucuronamide* **3f**: To a solution of 6,1-lactone **1** (100 mg, 331 μmol) in dichloromethane (1 mL) was added the dioctylamine **2f** (1.2 equiv). Then the reaction mixture was warmed at 40 °C. After total disappearance of the lactone followed by TLC, the crude reaction mixture was chromatographed on silica gel (ethyl acetate/cyclohexane 3:7) to give the corresponding glucuronamide **3f** as a colorless oil (131 mg, αβ:78/22).^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.56 (t, 1H, $J_{2-3} = J_{3-4} = 9.4$ Hz, H-3), 5.50 (d, 1H, $J_{1-2} = 3.6$ Hz, H-1), 5.49 (t, 1H, $J_{3-4} = J_{4-5} = 9.4$ Hz, H-4), 4.93 (dd, 1H, $J_{1-2} = 3.6$ Hz, $J_{2-3} = 9.7$ Hz, H-2), 4.83 (d, 1H, $J_{4-5} = 9.4$ Hz, H-5), 4.21 (br s, 1H, H-1CO*H*), 3.43–3.19 (m, 4H, $NCH_2 \times 2$), 2.10 (s, 3H, $COCH_3$), 2.04 (s, 3H, $COCH_3$), 1.97 (s, 3H, $COCH_3$), 1.60–1.46 (m, 4H, $NCH_2CH_2 \times 2$), 1.32–1.24 (m, 20H, $CH_2 \times 10$), 0.88 (t, 6H, $J = 6.9$ Hz, $CH_3 \times 2$). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.7, 170.3, 169.0 (3C, $COCH_3 \times 3$), 166.0 (C-6), 90.6 (C-1), 71.2 (C-2α), 70.3, 70.0 (2C, C-3, C-4), 65.6 (C-5), 47.6 (CH_2), 46.6 (CH_2), 31.9, 29.5, 29.3, 27.5, 27.0, 26.9, 22.7 (CH_2), 20.9, 20.8, 20.7 (3C, $COCH_3 \times 3$), 14.2 (2C, $CH_3 \times 2$). HRMS calcd for $C_{28}H_{49}NO_9Na^+$ $[M+Na]^+$: 566.3305 found *m*/*z*: 566.3313.
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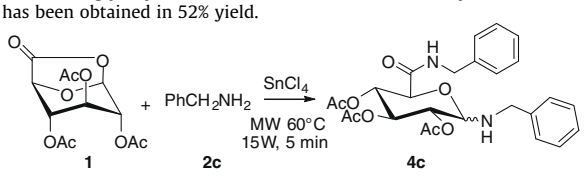
14. In the presence of a lewis acid catalyst, such as $SnCl_4$, both C-1 and C-6 can be substituted by benzylamine as showed previously for alcohols,[9] a one-pot amidification–glycosylation occurred. The benzamide–benzylamine derivative **4c** has been obtained in 52% yield.



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