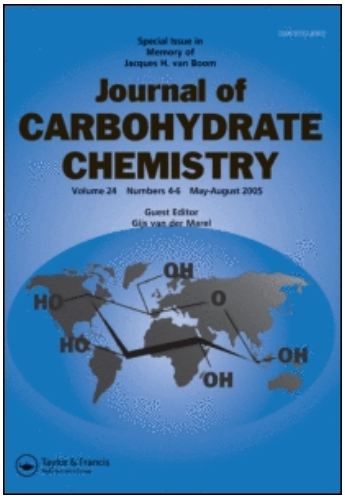

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COMMUNICATION

A ONE-POT SYNTHESIS OF GLYCOSYL AMIDES FROM GLYCOSYL AZIDES USING A MODIFIED STAUDINGER REACTION

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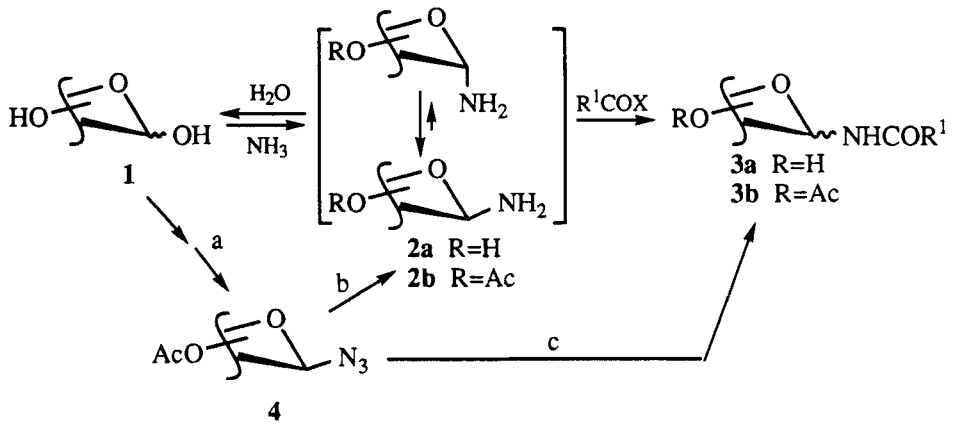
In a continuation of our research devoted to the synthesis and supramolecular assemblies of amphiphilic carbohydrates,[1-3] we report a new preparation of glycosyl amides β-**3a**. Interest in such compounds lies in their ability to escape glycosidases *in vivo* and in their use as potent nonionic biosurfactants. Several methods have already been reported in the literature for the preparation of such derivatives (Scheme 1).



Scheme 1

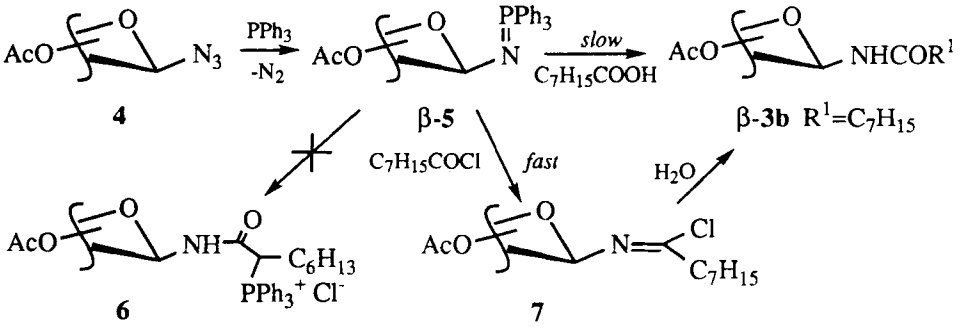
Direct methods to glycosyl amides involve acylation of glycosylamines **2a**. Despite an obvious simplicity, this method suffers from several disadvantages due to the instability of glycosylamines. As recently reinvestigated,[4] compounds **2a** must be synthesized following a very precise protocol. They hydrolyse very easily in neutral or acidic medium, the α/β anomerization is often difficult to control and they can dimerize spontaneously to form diglycopyranosyl amines.[4,5] Furthermore, the condensations of acylating agents with the latter display somewhat contradictory results.[4,6] Moreover, whereas the above syntheses can afford the expected derivatives **3a** without protection of the hydroxyl groups, the purification of the final compounds often requires acetylation, recrystallization (or chromatography) and de-*O*-acetylation, thus limiting the scope of the method.

Although additional steps are required, methods using fully acetylated glycosyl azide intermediates **4** are well designed for the syntheses of glycosyl amides **3**. The modes of preparation of the starting materials are numerous and well documented (pathway a);[7] they require two to three steps only and are high yielding and highly stereoselective to the 1,2-*trans*-glycopyranosyl azides. The syntheses of glycopyranosyl amides **3b** from **4** were most often reported via the reduction of the latter to the amine **2b** (pathway b: H_2/Pd-C, Raney Ni, PtO_2 or PPh_3/H_2O).[7] Nevertheless, the intermediate **2b** is endowed with the same inconveniences as its unprotected counterpart **2a**, to which one must add the possibilities of O → N acetyl migrations.

The Staudinger reaction, which was recently reviewed,[8] should allow direct condensation of a carboxylic acid with a glycopyranosyl azide (pathway c) without preliminary reduction of the azide. To our knowledge, one example only of such reaction was reported in the literature, *i.e.*, the reaction of protected L-aspartic acid with β-D-glucopyranosyl azides.[9] The reaction requires reactive phosphines (*e.g.*, triethyl phosphine), it is time consuming (several hours), the yields are strongly dependent on the structure of the glycosyl azide (from 77% with GlcNAc to 23% for Glc derivatives) and anomerization might sometimes occur.[10]

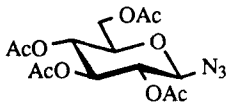
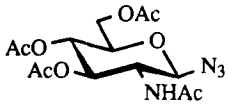
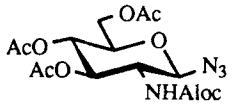
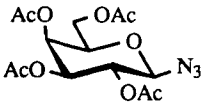
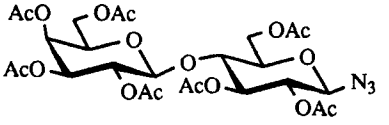
The synthesis described in the present paper uses a modified Staudinger reaction which strongly decreases the aforementioned inconveniences. In this variation, carboxylic acids are replaced by acid chlorides, as reported for the first time by E. Zbiral and E. Bauer.[11] The intermediates that can be expected when such reactions are effected on glycosylazides are most probably imidoyl chlorides **7**,[12] but *C*-phosphonium salts **6** may also form, as a few examples have been reported (Scheme 2).[13]

When they are formed, imidoyl chlorides **7** are hydrolyzed to the amide β-**3b** during the work-up procedure.



Scheme 2

Table. Acylation of glycopyranosyl azides in the presence of triphenylphosphine

Starting material (**4**)	Acylating agent	Solvent	**β-3b** (yield, %)[a]
	$C_7H_{15}COOH$	C_6H_6	no reaction
		CH_2Cl_2	no reaction
	$C_7H_{15}COCl$	C_6H_6	84
		CH_2Cl_2	90
	$C_7H_{15}COCl$	C_6H_6	67
		CH_2Cl_2	60
	$C_7H_{15}COCl$	C_6H_6	80
		CH_2Cl_2	52
	$C_7H_{15}COCl$	C_6H_6	72
		CH_2Cl_2	90
	$C_7H_{15}COCl$	C_6H_6	70
		CH_2Cl_2	60

a. Reactions were effected at room temperature, yields are given for compounds purified by column chromatography and are not optimized.

The reaction on several glycosyl azides was attempted with octanoyl chloride and octanoic acid, in the presence of triphenylphosphine, for comparison. The results are summarized in the Table.

As expected from results reported in the literature,[9] glycopyranosyl azides and octanoic acid did not react in the presence of triphenylphosphine. Nevertheless, an instantaneous reaction (nitrogen release) was observed when octanoyl chloride was used under the same conditions. After the work-up, glycosyl amides β-**3b** were formed as unique products with retention of the configuration at C-1. Retention of the initial stereochemistry could be attributed to a fast reaction leading to the glycosyl imidoyl chloride **7**, whereas the epimerization of the iminophosphorane β-**5** might occur at a slower rate.[14]

Among solvents used, benzene and dichloromethane afforded the best results, by comparison with dioxane. In toluene good yields of glycosyl amides were occasionally obtained (in the D-gluco series, for example), but they were dependent on the structure of the starting material **4**. The glycosyl phosphinimine intermediates β-**5** were formed in all solvents (as monitored by TLC and nitrogen release), although much more slowly and incompletely in dioxane. The heterogeneity of β-**5** solutions in dioxane, and sometimes toluene, seemed to decrease the rate of addition of the acid chloride on the glycosyl phosphinimine, by comparison with benzene and dichloromethane, thus limiting the yields of reactions.

De-*O*-acetylation of β-**3b** to β-**3a** ($R^1=C_7H_{15}$) was finally achieved in quantitative yield by the Zemplén procedure, without any anomerization.

This modified Staudinger reaction constitutes an efficient access to glycopyranosyl amides with a high control of anomeric stereoselectivity. Despite a greater number of steps than the direct methods using glycosylamines as starting materials, it affords the expected compounds under smooth conditions and with good yields. Furthermore, it uses an easily available and easy to handle phosphine. This method complements the straightforward aforementioned reactions, which are best suited for the preparation of derivatives possessing detergent properties. The main interest of this modified Staudinger reaction lies, in our opinion, in the possibility of *synthesizing* complex neoglycoplids by attachment of a fatty acid chloride with an oligosaccharide moiety, built from a glycosylazido derivative. The scope and limitations of the method are currently under investigation in our laboratory.

General experimental procedure. The glycosyl azide (1.0 mmol) and the acyl chloride (2.0 mmol) were dissolved in benzene or dichloromethane (4 mL). A solution of triphenylphosphine (1.2 mmol) in the same solvent (2 mL) was then added dropwise at room temperature. The reaction was instantaneous as can be judged by the violent

nitrogen release. The mixture was then diluted with chloroform and successively washed with a saturated aqueous $NaHCO_3$ solution and water, before drying and purification by column chromatography.

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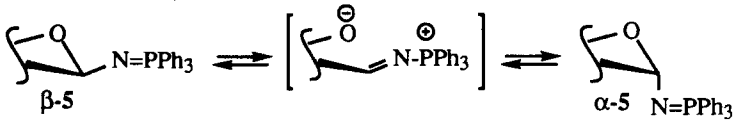
8. Y. G. Gololobov and L. F. Kasukhin, *Tetrahedron*, **48**, 1353 (1992).
9. T. Inazu and K. Kobayashi, *Synlett*, 869 (1993).
10. The glycosyl phosphinimine intermediate β-**5** can anomerize to α-**5** *via* an open-chain zwitterionic structure.



β-**5** α-**5**

11. E. Zbiral and E. Bauer, *Phosphorus*, **2**, 35 (1972).
12. M. D. Bachi and J. Vaya, *J. Org. Chem.*, **44**, 4393 (1979).
13. I. Bosch, A. Gonzalez, F. Urpi and J. Vilarrasa, *J. Org. Chem.*, **61**, 5638 (1996).
14. The formation of the *C*-phosphonium salts **6** cannot be excluded from our experiments. Nevertheless this side-reaction, if any, seems to constitute a very minor pathway.