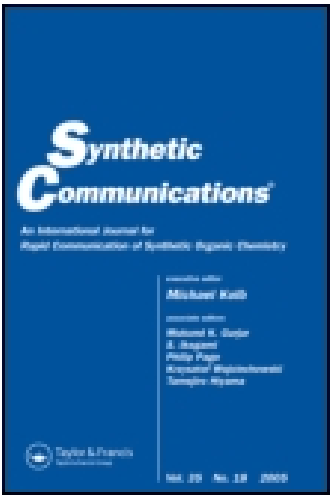

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Synthesis of Glucopyranosyl Amides Using Polymer-Supported Reagents

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Synthesis of Glucopyranosyl Amides Using Polymer-Supported Reagents

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ABSTRACT

2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl azide reacts efficiently with polymer-supported triphenylphosphine and various acid chlorides to yield glucopyranosyl amides with retention of the β-gluco stereochemistry.

Key Words: Glycosyl amides; Triphenylphosphine; Polymer-bound iminophosphorane; Polymer-supported Reagents.

Interest in the synthesis of glycosyl amides is inspired by the occurrence of this motif in naturally occurring biomolecules such as glycoproteins (e.g., **1**, Fig. 1)[1] and nucleic acids (e.g., **2**, Fig. 1). Glycosyl amides have been suggested as potential glycomimetics for the inhibition of glycosyl

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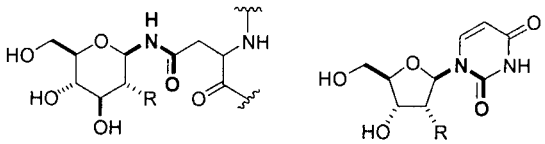


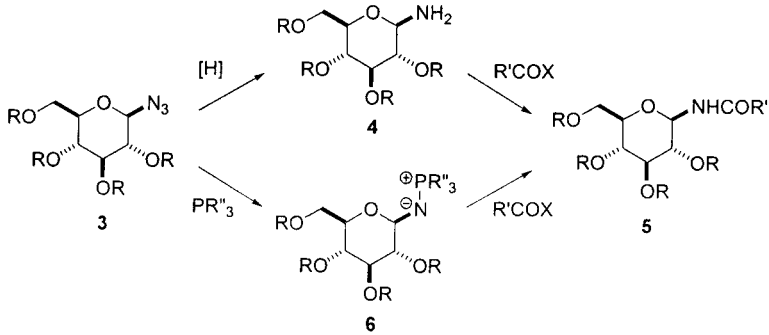
1 2

Figure 1. The glycosyl amide motif in biomolecules.

hydrolases[2] and as a useful linkage in the synthesis of glycosylated materials such as detergents.[3] Kunz and Pleuss have used *N*-glycosyl amides as precursors to glycosyl donors.[4] Notably, Murphy and coworkers have reported that synthetic glycosyl amide analogs have interesting biological properties, for example, as inhibitors of the binding of fibroblast growth factor (FGF-2) to heparin.[5]

Methods for the introduction of the glycosyl amide functionality (e.g., **5**, Sch. 1) have historically relied upon the formation of a glycosyl amine (**4**, Sch. 1), followed by coupling with a carboxylic acid (or derivative thereof).[6] However, this method is often complicated by anomeric interconversion resulting in lower anomeric stereoselectivity in the overall amide synthesis. Several groups have addressed this problem and shown that use of a Staudinger process,[3,5,7,8] in which a glycosyl azide (**3**, Sch. 1) reacts with a phosphine followed by reaction of the resulting iminophosphorane (**6**, Sch. 1) with a carboxylic acid derivative, is useful in that it avoids having to form the glycosyl amine.

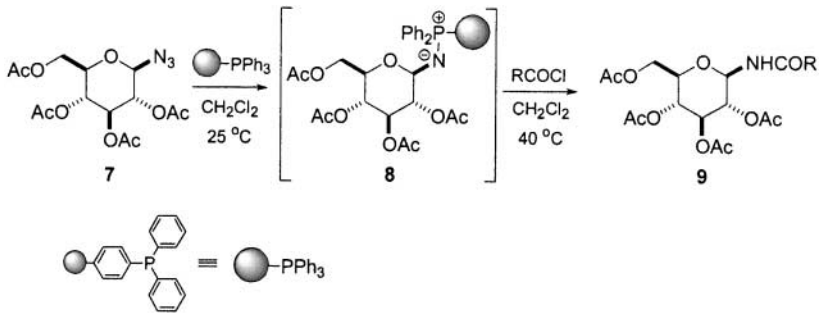
The choice of phosphine and carboxylic acid derivative are important, for example, using the parent carboxylic acids requires the use of trialkylphosphines such as PBu_3 since triarylphosphines do not result in conversion to



Scheme 1.

amides.[9] The latter may be used to generate the iminophosphorane if activated acid derivatives such as acid chlorides are employed,[3,8] and the resultant glycosyl amides are generally formed without anomerization during the reaction. Formation of triphenylphosphine oxide as a byproduct, however, may result in increased difficulties with product purification, for example, when using column chromatography. Potentially, the commercially available polystyrene-supported triphenylphosphine (PS-PPh_3) could be used in this chemistry, thus avoiding problems with workup. Applications of PS-PPh_3 in related Staudinger-type chemistry have been reported,[10] and results compare favorably with the use of PPh_3 with the ease of workup making the former reagent attractive. To investigate the application of polymer-supported reagents in the rapid synthesis of glycosyl amides, we have studied the reaction of 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl azide (**7**, Sch. 2)[11] with PS-PPh_3 and various acid chlorides using a parallel synthesizer to generate a small library of glucosyl amides (**9**, Sch. 2). Several of the amides have also been made using PPh_3 to compare results and reaction times.

Using the FirstMate parallel synthesizer,[12] each reaction vessel was charged with 1 equiv. of azide **7**, 2 equiv. of acid chloride (Table 1), and then PS-PPh_3 was added, and the reaction mixture agitated at room temperature until the evolution of gas had ceased. The mixtures were then refluxed for 6 hr, the polymer filtered, and the filtrate treated with polymer-supported *tris*(2-aminoethyl) amine to remove the excess acid chloride. Filtration and evaporation of the solvent gave the amide products **9a**–**l** in the yields shown in Table 1. Analysis of the residues by ^{1}H NMR showed that the glycosyl amide was formed in most cases, and that the purity of the products was generally >85%. Further purification is possible by eluting the amides through a short silica gel column, which gave material of sufficient purity for analysis.



Scheme 2.

The results in Table 1[a] give a general picture for the reactivity of acid chlorides in this chemistry. In all cases, the starting azide **7** was consumed after the PS-PPh_3 was added, as seen from TLC analysis of the reaction mixture, and after 6 hr at 40°C only two reactions, that of **7** with PS-PPh_3 and pyrrolidinoyl chloride (entry **g**, Table 1) and that of **7** with PS-PPh_3 and pivaloyl chloride (entry **i**, Table 1), failed to provide any amide product. The azide was consumed in both cases, but little or no carbohydrate product was isolated, which indicates that the intermediate (now polymer-bound) iminophosphorane does not react efficiently with these acid chlorides under these conditions. The highest yield, i.e., for the formation of the *p*-nitrobenzoyl amide **9a**, suggests that the polymer-bound iminophosphorane reacts most efficiently with highly electrophilic acid chlorides. Furthermore, the lack of an amide product from reaction with pivaloyl chloride indicates that the large *t*-butyl substituent retards the rate of reaction between the polymer-bound iminophosphorane and acid chloride. The remainder of the carbohydrate material is presumably still attached to the polymer support.

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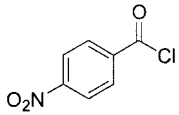
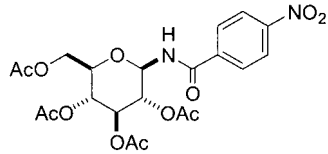
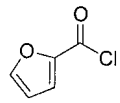
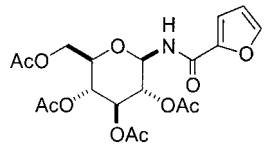
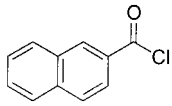
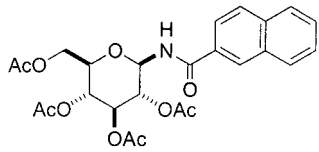
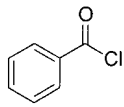
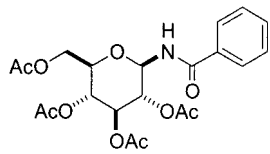
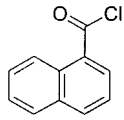
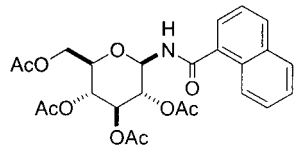
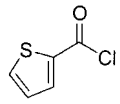
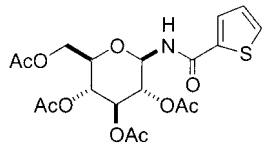
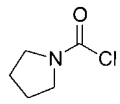
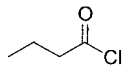
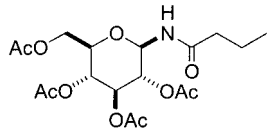
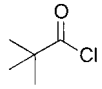
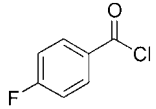
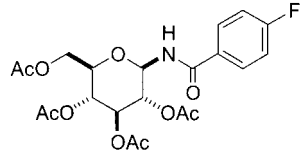
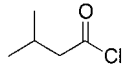
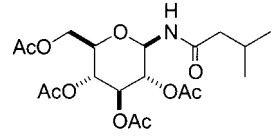
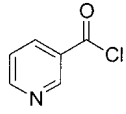
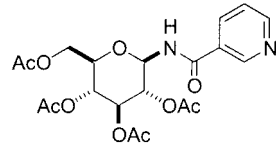
[a]All new compounds were homogeneous by TLC and at least 95% pure as indicated by ^{1}H NMR spectra. All compounds gave satisfactory analytical data, including ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz), and mass spectra. Typical procedure for the formation of glucopyranosyl amides using polymer-supported triphenylphosphine: D-glucosyl azide **7** (100 mg, 0.27 mmol) and *p*-nitrobenzoyl chloride (0.54 mmol) were dissolved in CH_2Cl_2 (5.0 mL). Polymer-supported triphenylphosphine (~3 mmol/g loading, 116 mg, ~0.35 mmol) was added to the tube, and the mixture was agitated until the release of nitrogen gas had ceased. The mixture was then agitated and refluxed gently for 6 hr. The mixture was cooled, gravity filtered into another test tube to remove polymer-supported triphenyphosphine oxide, which was washed with CH_2Cl_2 (2 × 5 mL). Polystyrene-bound *tris*(2-aminoethyl) amine (4.0–5.0 mmol/g loading, 200 mg, ~0.88 mmol) was added to the solution, and the mixture was agitated for 2 hr at room temperature. The polymer was removed via gravity filtration, washed with CH_2Cl_2 (2 × 5 mL), and the filtrate was concentrated in vacuo to leave the product residue. Physical characteristics for amide **9a**: 400 MHz ^{1}H NMR ($CDCl_3$) δ 2.03, 2.04, 2.05 (3s, 12H total, 4 × $COCH_3$), 3.91 (m, 1H, H-5), 4.09 (dd, 1H, H-6, $J = 1.83$, 12.45 Hz), 4.31 (dd, 1H, H-6′, $J = 4.39$, 12.08 Hz), 5.05 (m, 2H, H-3, H-4), 5.39 (m, 2H, H-1, H-2), 7.32 (d, 1H, NH, $J = 9.15$ Hz), 7.92 (d, 2H, Ar-H), 8.30 (d, 2H, Ar-H). 100 MHz ^{13}C NMR ($CDCl_3$): δ 21.97, 62.63, 69.18, 72.09, 73.41, 74.87, 80.06, 124.96, 129.40, 129.60, 139.08, 151.05, 166.04, 170.77, 171.52, 172.84. Mass calculated: 497.15. Found: 497.18. $[\alpha]_D^{20}$ -19.3 (*c* 5.1, CH_2Cl_2). TLC R_f-values for glycosyl amides (aluminum-backed silica gel plates using 1 : 1 EtOAc/hexane as eluent and visualization with 5% H_2SO_4 in ethanol followed by heating on a hot plate): **9a**, 0.72; **9b**, 0.66; **9c**, 0.69; **9d**, 0.70; **9e**, 0.70; **9f**, 0.70; **9h**, 0.60; **9j**, 0.69; **9k**, 0.66; **9l**, 0.36.

Table 1. Glucopyranosyl amides synthesized via Sch. 2.

Entry	Acid chloride	Amide product	Yield (%)
a			93
b			40
c			72
d			55
e			66
f			56
g		—	—
h			61

(*continued*)

Table 1. Continued.

Entry	Acid chloride	Amide product	Yield (%)
i		—	—
j			61
k			60
l			40

Treatment of azide **7** with PPh_3 in the presence of *p*-nitrobenzoyl chloride, 2-furoyl chloride, benzoyl chloride, and thiophene-2-carbonyl chloride according to Boullanger's method[3] afforded amides **9a** (95% yield), **9b** (90% yield), **9d** (81% yield), and **9f** (92% yield) respectively, after only 30 min at room temperature. Purification required flash chromatography in each case to separate the amide product from $Ph_3P{=}O$; thus, there is a trade-off between the ease of purification in the polymer-supported chemistry and the longer reaction times required, a drawback that has been noted by others previously.[13] The use of polymer-supported triphenylphosphine is, however, amenable to parallel synthesis, where many related compounds may be produced in the search for novel glycosyl amides with potentially useful biological activity.

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