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A facile stereoselective synthesis of α-glycosyl ureas

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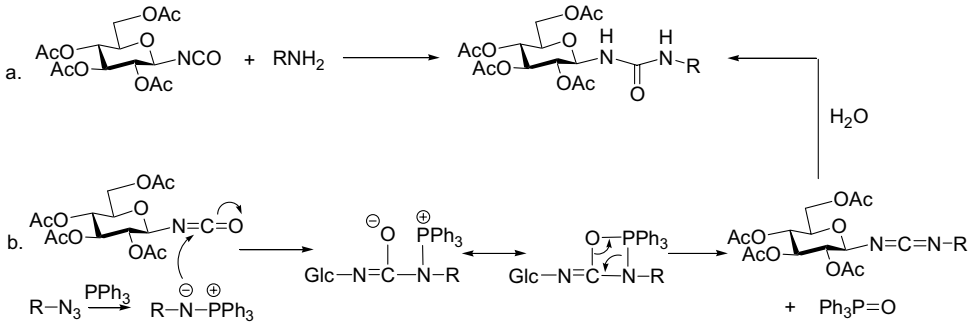
Abstract—α-Glycosyl ureas can be synthesised directly from tetra-*O*-benzyl glycosyl azides and isocyanates, using a one-pot procedure that is simple and general in scope. The benzyl protecting groups are easily removed from the urea products by catalytic hydrogenation. The synthesised α-glycosyl ureas represent a new class of neo-glycoconjugates with the potential of being resistant towards carbohydrate processing enzymes.

Keywords: Carbohydrates; Glycosyl azides; Glycosyl ureas; Neo-glycoconjugates; Synthetic methods

1. Introduction

Glycosyl ureas are found in nature in the aminoglycosidic antibiotics.[1,2] They have also been used as stable N-linked-glycopeptide mimics[3] and for the synthesis of polyvalent glycoconjugates.[4] However, only a few methods for the synthesis of glycosyl ureas have been reported,[5–8] and in particular, a practical synthesis of anomeric α-glycosyl ureas is still lacking.[3b,7d] Yet, these compounds could constitute an interesting new class of neo-glycoconjugates, with virtually unexplored physical and chemical properties and biological activity. In fact, because glycosyl derivatives can be highly sensitive to chemical or enzymatic hydrolysis, it is particularly interesting to have access to new modified structures that could be endowed with an increased stability.

Glycosyl ureas are generally prepared starting from glycosyl isocyanates (Scheme 1).[7,8] These substrates can react directly with amines[7] (Scheme 1a) or with iminophosphoranes[8] generated by reduction of azides[9] (Scheme 1b). In the latter case, carbodiimides are initially obtained and subsequently hydrolysed to the cor-



Scheme 1. Synthesis of β-glycosyl ureas from glycosyl isocyanates: (a) direct synthesis using amines,[3,7] (b) synthesis via carbodiimides, using iminophosphoranes.[8]

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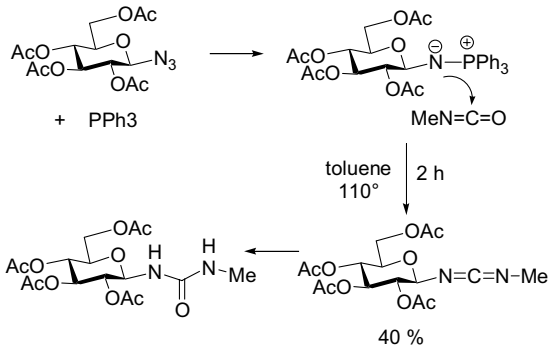


Scheme 2. Reaction of tetra-*O*-acetyl-glucopyranosyl iminophosphorane with isocyanates.[8a]

responding ureas, most conveniently in a one-pot procedure (Scheme 1b).[8a] The starting glycosyl isocyanates can be synthesised either from glycosyl halides, following the classical Fischer procedure,[6] or from the corresponding azides,[3,7] using multi-step sequences that involve glycosyl isonitriles[3,7a–c] or glycosyl carbamates[7d] as intermediates. The stereoselectivity of these transformations is complete for β azides, but 4:1 α/β ratios are typically obtained starting from the α anomers.[7]

Direct conversion of glycosyl azides to ureas could in principle be achieved by inverting the reaction partners of the carbodiimide reaction, as shown in Scheme 2. Thus, a glycosyl azide could be transformed with phosphines into a glycosyl iminophosphorane, which could react with isocyanates to give ureas through a carbodiimide intermediate (Scheme 2).

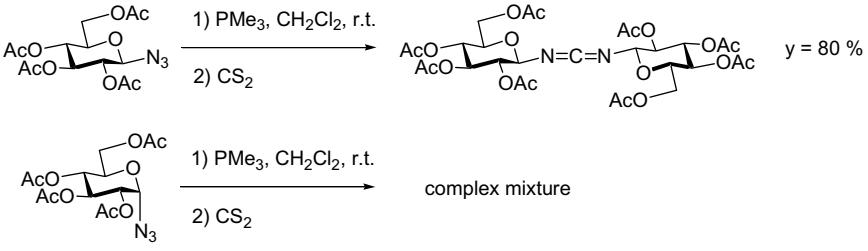
However, in practice,[8a] anomeric glycosyl iminophosphoranes of tetra-*O*-acetyl pyranoses react very sluggishly with isocyanates.[8a] For instance, at room temperature no reaction occurred between 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl phosphinimine and methyl isocyanate, while at 110 °C the reaction proceeded in two hours in low yield (Scheme 2). With more complex isocyanates, the reaction is even slower and gives rise to various side products.[8a]

In a recent example, Györgydeák and co-workers employed a similar procedure for the synthesis of symmetrical and unsymmetrical glycosyl carbodiimides.[10] The reaction of peracetylated glycosyl azides with 1 equiv of trimethylphosphine in dry dichloromethane at room temperature led to the corresponding iminophosphoranes. The in situ reaction of these compounds with carbon disulfide under mild conditions led to the symmetrical glycosyl carbodiimides. The procedure worked effectively starting from β-azides and the expected products were obtained in good yields as stable crystalline solids. However, from α-azides, complex reaction mixtures were formed and the expected products could not be isolated (Scheme 3).

Here we report that, on the contrary, 2,3,4,6-tetra-*O*-benzyl-glycosyl azides give iminophosphoranes that do react productively with isocyanates without anomeric isomerisation. Hence, a one-pot stereoselective synthesis of α-glycosyl ureas from α-glycosyl azides can be easily achieved, provided that tetra-*O*-benzyl α-glycosyl azides are used as starting material.[11] The benzyl protecting groups are then simply removed from the urea products by catalytic hydrogenation. In general, the resulting α-glycosyl ureas were found to be configurationally stable, but one exception was found. Thus, a new class of neoglycoconjugates becomes available for further studies.

2. Results and discussion

The low reactivity observed for anomeric glycosyl iminophosphoranes is likely due to the electron withdrawing effect of the pyranose moiety, which stabilises the negative charge on the ylide nitrogen (Scheme 2) and reduces its nucleophilicity.[8a] This effect is maximised for acetylated (disarmed[12]) pyranoses but it should be greatly reduced if the hydroxyl groups of sugar are protected as benzyl ethers (armed[12]). Therefore, we reasoned that the iminophosphoranes obtained by reduction of the 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl azide **1**[11a,13] (Scheme 4) ought to react with alkyl isocyanates. The reaction of **1** with triphenylphosphine in dry dichloromethane at room temperature followed by treatment with benzyl isocyanate afforded a complex mixture of reaction intermediates that contained the α anomer of carbodiimide **2** (20% yield). The reaction of **1** with trimethylphosphine was much faster. After disappearance of the starting material, benzyl isocyanate was added to the mixture and complete conversion of the intermediate into the corresponding carbodiimide **2**



Scheme 3. Synthesis of symmetrical carbodiimides from tetra-*O*-acetyl-glucopyranosyl azides.[10]