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Efficient Synthesis of Glycoporphyrins by Microwave-Mediated "Click" Reactions

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The Cu^{I}-catalysed Huisgen cycloaddition "click" reaction has been applied to the synthesis of a range of triazole-linked glycoporphyrins. The "click" reaction under microwave-heating conditions has been shown to provide a general and robust methodology for the synthesis of mono-, di-, tri- and tetra-modified glycoporphyrins. A sequential "double-click" process was employed to access a new class of bis-modified 5,10-diglycoporphyrins displaying heterogeneous carbohydrates.

Introduction

Glycoporphyrins offer fascinating prospects for medicinal chemistry and glycobiology.[1a–1d] Carbohydrates not only improve the solubility of porphyrins in an aqueous environment, but also offer improved targeting of porphyrin therapeutics.[2] For photodynamic therapy (PDT),[3] carbohydrates can bind to tumour-associated lectins displayed on the surface of cancer cells therefore offering the potential for enhanced efficiency and improved selectivity in cancer treatment. Because lectin–carbohydrate interactions are relatively weak it would be advantageous to have access to a PDT photosensitiser with a defined cluster displaying more than one carbohydrate unit. Even more advantageous would be a defined system that displays more than one "type" of carbohydrate. The synthesis of selectively modified, heterogeneous glycoporphyrins has not previously been reported. To date, the synthesis of glycoporphyrins has relied predominantly on the condensation reaction between a glycosylated aldehyde and a glycosylated aldehyde and a pyrrole.[4a–4c] This reaction is often low yielding and is unsuitable for systems where small quantities of a carbohydrate are available. A more general strategy involves the introduction of carbohydrates at specific sites predefined by a regioselective chemical modification.[5] A number of methodologies for the functionalisation of porphyrins with carbohydrates have been investigated including the use of Sonogashira[6] and olefin metathesis[7] cross coupling.

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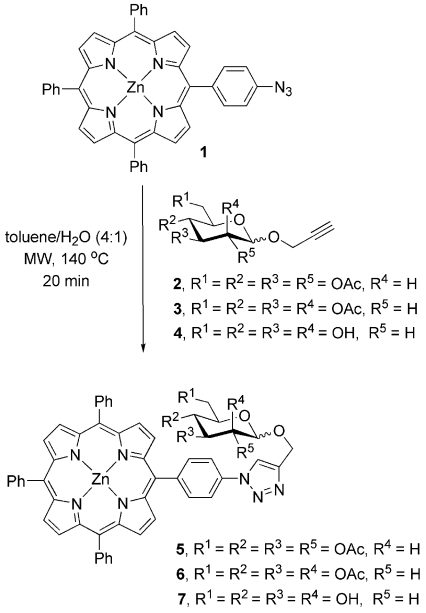
Results and Discussion

For this study we chose to investigate if the Cu^{I}-catalysed 1,3-dipolar "click" reaction[8] could be employed as a robust methodology to access a highly defined, multifunctionalised glycoporphyrin system.

Click chemistry has previously been applied to the functionalisation of porphyrins,[9a–9b] but to date there are few literature examples describing a "click" reaction between a carbohydrate and a porphyrin or chlorin.[10] Recently, Vicente and co-workers have employed a "click" methodology for the preparation of glycoporphyrins displaying either one or four galactose or lactose moieties, carbohydrate functionalised tetrabenzoporphyrin (TBP) was found to be efficiently uptaken by human carcinoma Hep2 cells.[11] Hasegawa and co-workers have applied "click" chemistry to the preparation of octaglycosylated porphyrins.[12] 5,10,15,20-Tetraphenylporphyrin was chosen as a common starting material for all modifications. This symmetrical porphyrin can be readily accessed in good yield via a condensation reaction of benzaldehyde and pyrrole. Porphyrin derivative **1**, displaying a single azide was prepared according to the literature procedure.[12] The coupling reaction with commercially available β-propargyl glucose **2** (Scheme 1) was investigated under both conventional and microwave-mediated heating. The use of MW heating conditions reduced the reaction time from 3 d to 20 min. A range of reaction conditions were screened. The results of this initial study are outlined in Table 1.

It was found that copper chloride in toluene/water (4:1) at 120 °C for 20 min furnished the desired mono-glycoporphyrin **5** in excellent yield (93%). THF/water (4:1) also gave a very good yield of 81% at a lower temperature but longer times (40 min) were required for complete consumption of the starting material. It was found that zinc porphyrin was required for "click" conditions in order to avoid complex formation with the copper catalyst.



Scheme 1. Synthesis of mono-glycoporphyrin by microwave-mediated "click" reaction.

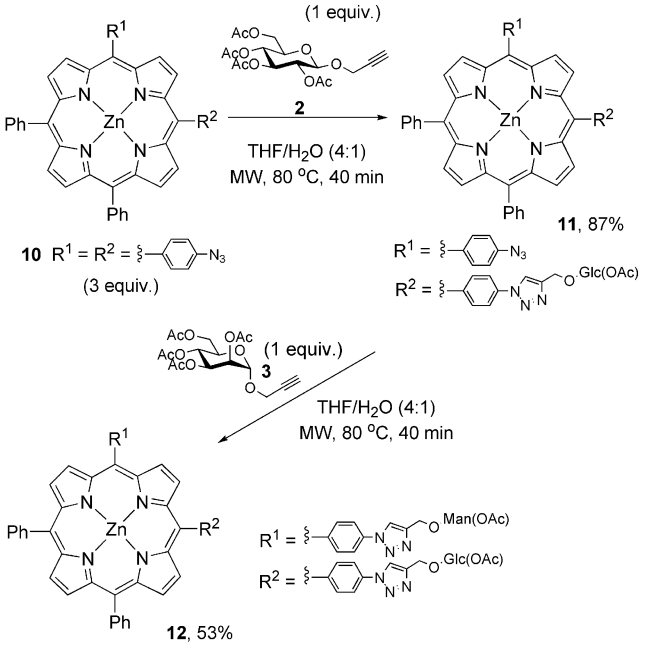
Table 1. Optimisation of conditions for Cu-catalysed click reaction.

Entry	Sugar catalyst[a]	Solvent[b]	Temp.[c]	Yield (%)[d]
1	**2** CuCl	toluene	90–140	47
2	**2** CuCl	toluene	140	85
3	**2** CuCl	toluene/H_2O	140	93
4	**2** CuBr	toluene/H_2O	140	78
5	**2** CuI	toluene/H_2O	140	44
6	**2** $CuSO_4$, Na^+ ascorbate	toluene/H_2O	140	89
7	**2** CuCl	DMSO/H_2O	140	67
8	**2** CuCl	DMSO/H_2O	160	63
9	**2** CuCl	DMSO/H_2O	160	52
10	**2** CuCl	THF/H_2O	80	81
11	**2** CuCl	DMF/H_2O	140	74

[a] Catalyst loading was 30%. [b] Where two solvents were used ratio was (4:1). [c] Temperatures were obtained under microwave heating for 20 min. [d] Isolated yield.

The reaction was repeated with α-propargyl mannose, prepared according to the literature procedure,[13] and the desired mannosylated glycoporphyrin **6** was isolated in 91% yield. A fully deprotected mannosyl residue **4** was also introduced via the "click" reaction to furnish **7** in good yield 61%. This reaction highlights the potential for the introduction of unprotected oligosaccharides isolated from natural sources using this methodology. It also means that deprotection reactions, which can be low yielding for oligosaccharides can be carried out prior to functionalisation of the porphyrin. The fact that the glycoporphyrin was easily visible on the chromatography column facilitated the rapid and simple purification of the glycoconjugate displaying the fully deprotected sugar.

The next step was to investigate if the methodology could be applied to diazidoporphyrins. Nitration of 5,10,15,20-tetraphenylporphyrin furnished the 5,10 and 5,15 regioisomers in a 2:1 ratio and offers an alternative entry to the 5,10-disubstitution pattern in porphyrins (Scheme 2).[14a,14b] These compounds were easily separated by column chromatography. They were both subsequently converted into the corresponding (azidophenyl)porphyrins after reduction of the nitro groups were achieved. The click reaction using two equivalents of the propargyl glucose worked efficiently and the 5,10-diglycoporphyrin **8** was isolated in 80% yield and the 5,15 compound **9** in 75% yield. This ability to control the relative position of carbohydrate side chains on the porphyrin may have very important consequences for lectin binding.



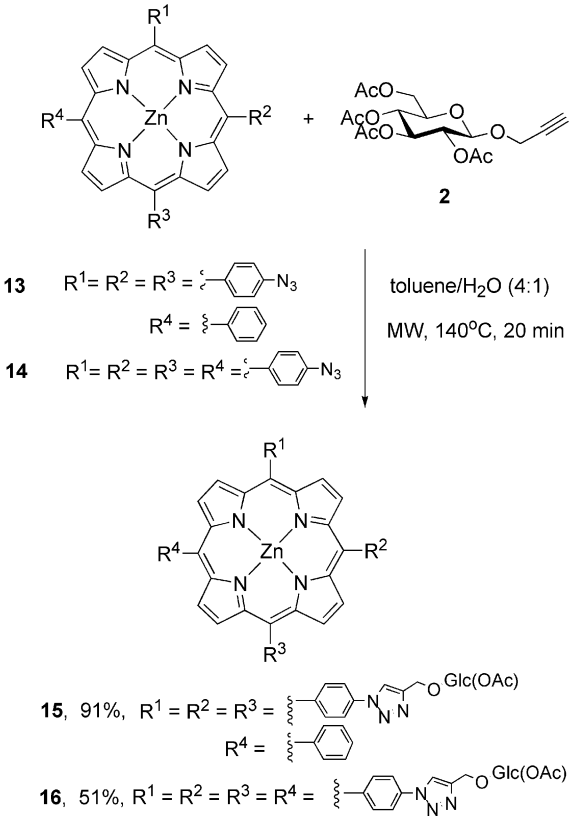
Scheme 2. Synthesis of 5,10-bis-modified heterogeneous glycoporphyrin via stepwise "double click" reaction.

Efficient, regioselective synthesis of bis-modified glycoporphyrins has not previously been described. It was determined that a sequential "double click" reaction where one carbohydrate moiety was introduced followed by addition of a second onto the "latent" azide could be achieved.

Reaction of propargyl glucoside **2** with three equivalents of diazaporphyrin **10** furnished the glycoporphyrin **11** as the sole product isolated in very good yield 87%. The propargyl mannoside **3** was then introduced via a second sequential click reaction to furnish the bis-modified glycoporphyrin **12** in 53% yield.

In order to avoid reduction of the "latent" azide and allow the stepwise process to occur, the amount of copper catalyst had to be carefully controlled. It was found that 30% catalyst loading was optimum for each step of the "double click" reaction. The excess porphyrin required for the first click reaction was recovered almost quantitatively by column chromatography making this an efficient process. The scope of this reaction is not just limited to carbohydrates and studies are currently underway to prepare mixed porphyrins functionalised with carbohydrates, lipids and amino acids.

Following the successful preparation of the bis-modified product, the tri- (**13**) and tetraazido (**14**) porphyrins were synthesised. The conditions employed for the mono- and dimodification were repeated, using three and four equivalents of the propargyl glycoside, respectively. The tri- (**15**) and tetraglycosylated porphyrins (**16**) were both isolated in good to moderate yields, respectively (Scheme 3). This demonstrated that the same general conditions could be used to prepare the mono-, di-, tri- and tetra-functionalised glycoporphyrins. This suggests that the methodology could even be applied to the synthesis of dendritic glycoporphyrins displaying a large number of carbohydrate side chains. It should be noted that while the conditions for **15** and **16** are unoptimised, the yield of **16** is considerably lower, most likely due to solubility issues with the azaporphyrin **14**.



Scheme 3. Synthesis of tri- and tetra-substituted glycoporphyrins.

Conclusions

The "click" reaction under microwave-heating conditions represents an efficient and robust methodology for the synthesis of defined glycoporphyrins amenable for further elaborations. General conditions were determined for the introduction of homogeneous carbohydrates and conditions for the stepwise bis-modification with heterogeneous carbohydrates were also determined. The methodology has been optimised to allow functionalistion of the tetrapyrrole core with both protected and fully deprotected carbohydrates. Studies are currently underway to explore additional, orthogonal modification strategies including cross metathesis and organometallic coupling reactions for the construction of highly diverse glycoporphyrins and analogues. Carbohydrate sequences suitable for binding tumour associated lectins will be introduced using this methodology. Biological assays to study the therapeutic applications of these systems are also under investigation.

Supporting Information (see also the footnote on the first page of this article): General experimental procedures and complete characterisation data of all products, ^{1}H and ^{13}C NMR spectra.

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