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Selective Deprotection of Trityl Group on Carbohydrate by Microflow Reaction Inhibiting Migration of Acetyl Group

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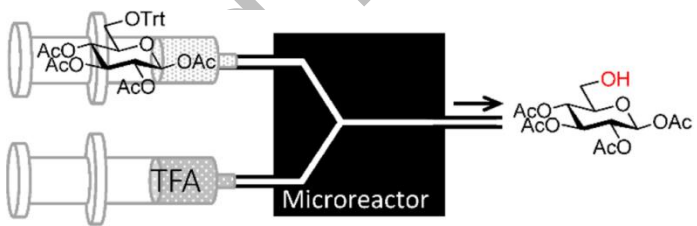
Abstract

The trityl group is an important and useful protecting group for primary hydroxy groups on carbohydrates. However, during deprotection, neighbouring acetyl groups can easily migrate to the deprotected hydroxy groups. Hence, deprotection of trityl groups was optimised using a microreactor with regard to flow rate, reagent concentration, reaction time, and substrate concentration. The optimised microflow reaction conditions inhibited migration and could be applied to large-scale reactions and other substrates.



KEYWORDS: Microreactor; Reaction optimization; Deprotection; Trityl group; Carbohydrate

INTRODUCTION

In carbohydrate chemistry, the introduction of protecting groups to hydroxy groups on sugars is important for regioselective reactions, and subsequent selective deprotection of the protecting groups is imperative as well.[1–4] Hexoses contain three types of hydroxy groups: primary, secondary, and hemiacetal. To protect these hydroxy groups, various protecting groups have been developed and utilised for the synthesis of oligosaccharides and carbohydrate analogues. In particular, the primary hydroxy group is protected selectively by bulky functional groups. Trityl and *tert*-butyl diphenyl silyl (TBDPS) groups, which are deprotected under acidic conditions, were often used along with acyl groups for protection.[5–10] However, a problem sometimes arises during deprotection. In the case of 1,2,3,4-tetra-*O*-acetyl-6-*O*-trityl-β-glucose, after deprotection of the trityl group the deprotected hydroxy group at the 6-position attacks the carbonyl of the acetyl group at the 4-position, and then, the acetyl group migrates to the 6-position.[6,11–14] Although deprotection is completed in a short time, acetyl migration often occurs because the product undergoes this intramolecular side-reaction. Moreover, separation by silica gel chromatography is difficult because the R_f value of the product is similar to that of the migrated by-product. However, protection of primary hydroxy groups by trityl groups is effective for the formation of 1,6-glycosidic bonds in synthesis of polysaccharides such as

β-glucans and mannans and for selective modification at the 6-position.[15_18] Therefore, development of the inhibition method of acyl migration is expected.

Recently, flow chemistry using a microreactor has been applied to multistep and selective reactions.[19–26] Flow reactions in the microfluid channel have advantages: uniform mixing of reagents, easy control of flow rate, reaction time, temperature, high reproducibility, and facile scale-up.[27–30] It has been reported that reactions which were not sufficiently selective or efficient in the flask gave high selectivity and yield by microflow reaction. For example, Kawaguchi et al. reported that Swern–Moffatt oxidation proceeded at room temperature in a very short reaction time by avoiding the decomposition of highly reactive intermediates using a microreactor.[31] Seeberger and co-workers worked on the synthesis of oligosaccharides using conditions which were optimised by microflow reaction.[32–34]

In this study, a microflow reaction was utilised for the efficient deprotection of a trityl group on 6-trityl acetyl glucose, which is an important intermediate in the synthesis of glucose analogues and oligosaccharides. By using a microreactor, the substrate and

reagent were mixed uniformly and the reaction time was shortened, inhibiting side-reactions.

RESULTS AND DISCUSSION

Firstly, the ratio of the product to by-products produced by deprotection in the flask was investigated. 1,2,3,4-Tetra-*O*-acetyl-6-*O*-trityl-β-D-glucose (**1**) was dissolved in 15% trifluoroacetic acid (TFA) in CH_2Cl_2, and stirred at room temperature for 10 min. After confirming the depletion of **1**, the solution was quenched, washed, and dried *in vacuo*, and then the ^{1}H NMR spectrum of the residue was measured to analyse the ratio of compounds **1**–**3** (Scheme 1).[6] The ratio was calculated using each of the integrated values in the ^{1}H NMR spectrum (Fig. 1).

The results showed that the product (**2**) and by-product (**3**), in which the acetyl group had migrated to the 6-hydroxy group, were obtained in 84% and 13% yield, respectively. **3**, which was hardly detected in TLC analysis after 10 min into the reaction, increased during analysing the reaction by TLC. Additionally, TLC analysis using hexane:ethyl acetate = 1:2 indicated that the R_f values of **2** and **3** were similar (0.45 and 0.48, respectively). It was difficult to isolate the products efficiently by silica gel chromatography, and thus, **2**

was isolated in 41% yield by recrystallisation. To obtain **2** in high yield, trityl deprotection, which can avoid the migration of **2**, is required. Therefore, a reagent which rapidly depleted **1** was sought by TLC analysis. The reagents tested were acetic acid,[35] cation exchange resin,[36] 4 M HCl in dioxane,[37] 50% TFA in CH_2Cl_2,[15,38] $CuSO_4$[39] and Pd/C with H_2 gas.[4] From the results, 50% TFA in CH_2Cl_2 was selected as the optimal reagent for the microflow reaction because **1** depleted quickly in comparison to other reagents (within 10 min) to afford **2** and a slight amount of **3**. The flow rate, concentration of TFA, reaction time, and concentration of **1** were optimised for the microflow reaction. The microreactor used in this study was a Y-shaped flow channel linked *via* tubes with two syringe pumps (Fig. 2). The yields of each compound were calculated from the integration values of ^{1}H NMR.

The optimal flow rate for uniform mixing of the solution of **1** in CH_2Cl_2 and TFA in CH_2Cl_2 was investigated, and the reproducibility was evaluated over three experiments. The reaction conditions were as follows: concentration of **1**, 85 mM; reagent, 2.5% TFA in CH_2Cl_2; reaction time, 7.5 s; flow rate, 0.1, 1.0, 3.0, and 9.0 mL/min. As shown in Fig. 3 (a), the yield of **2** was almost same at 1.0, 3.0 and 9.0 mL/min. High reproducibility and

uniform mixing of the solutions were obtained for flow rates above 3.0 mL/min (Fig. 3 (b)). From these results, 9 mL/min was selected as the optimal flow rate for efficiency.

TFA is often used for deprotection but is a very strong acid. Therefore, compounds should be soaked in TFA solution for only a short time. Thus, optimisation of TFA concentration was carried out. The reaction conditions were: flow rate, 9.0 mL/min; concentration of **1**, 85 mM; reaction time, 7.5 s, and various concentrations of TFA (2.5, 5, 10, and 15% TFA in CH_2Cl_2) were used to investigate the efficient conversion of **1**. The results in Fig. 4 indicate that **2** was obtained in a more efficient manner with increasing TFA concentration. When the concentration of TFA was above 10%, **1** and by-product **3** were little. Therefore, 10% TFA in CH_2Cl_2 was selected as the optimal concentration because the reaction mixture must be neutralised after running through the tube.

To investigate the optimal reaction time for inhibiting migration, reaction times of 0.07, 0.75, 7.5, 17.8, 41.1, and 120 s were examined, using the following reaction conditions: flow rate, 9 mL/min; concentration of **1**, 85mM; concentration of TFA, 10% TFA in CH_2Cl_2. The reaction time is the time taken for the solution to flow through the tube after mixing in the microchannel. The results indicated that the majority of **1** depleted after 7.5

s and the amount of migrated by-product **2** increased with a longer reaction time (Fig. 5). Therefore, 7.5 s was selected as the optimal reaction time.

Using the optimised conditions (flow rate: 9.0 mL/min; concentration of TFA: 10% TFA in CH_2Cl_2; reaction time: 7.5 s), the optimal concentration of **1** (25, 85, 150, 300, and 638 mM) was investigated for scale-up. As shown in Fig. 6, an 85 mM solution of **1** reacted in over 98%, whereas the conversion efficiency of a 150 mM solution of **1** decreased significantly. These results indicated that the microreactor with Y-shaped flow channel is suitable for the mixing of a solution of **1** of below 85 mM.

The optimised conditions were therefore: flow rate, 9.0 mL/min; concentration of TFA, 10% TFA in CH_2Cl_2; reaction time, 7.5 s; concentration of **1**, 85 mM. Under these conditions, 4.5 g of **1** was deprotected with a slight amount of **2** produced in the microreactor, and the crude product was purified by silica gel column chromatography to give the final product in 90% yield. The obtained high yield results from efficient conversion of the starting material and the inhibition of migration by microflow reaction under the optimised conditions.

The optimised reaction was then applied to other sugars, **4** and **5** in Fig. 7. Deprotection of the trityl group on 1,2,3,4-tetra-*O*-acetyl-6-trityl-*O*-mannose (**4**) was successfully performed using the optimised microflow reaction conditions. Surprisingly, analysis of the reaction by ^{1}H NMR indicated that it proceeded quantitatively without migration. Next, a laminaribiose derivative (**5**) was detritylated under the same conditions. ^{1}H NMR analysis of the reaction revealed that the by-product was not detected and the disaccharide was also detritylated quantitatively. These results were better than those for glucose and therefore demonstrated that this method is a useful technique for the detritylation of sugars containing acetyl groups.

CONCLUSION

Optimal conditions for the deprotection of trityl groups by microflow reaction were investigated and acetyl migration to neighbouring positions was inhibited to afford the desired product in excellent yield. Moreover, a large-scale reaction was carried out using the microreactor and the product was isolated in 90% yield by column chromatography. Additionally, trityl groups on mannose and laminaribiose derivatives were deprotected quantitatively. This method can deprotect trityl groups efficiently at the 6-position in sugars and makes trityl group protection easier to handle in carbohydrate synthesis.

Consequently, the construction of polysaccharides containing 1,6-glycosidic bonds and functionalisation of the 6-position of sugars for biological applications will be accessible.

EXPERIMENTAL

General Procedure For Optimisation Of The Reaction In The Microreactor

The microreactor and two syringe pumps with 3 or 30 mL syringes (A and B, respectively) were linked *via* PTFE tubes for the optimised reaction. Solutions dissolved substrate in CH_2Cl_2 (solution A) and dissolved reagent in CH_2Cl_2 (solution B) were set in separate syringes. Solutions A and B were flowed at the same flow rate using syringe pumps and mixed *via* the microreactor. The mixture was poured into aqueous saturated $NaHCO_3$ to neutralise the reagent and extracted with CH_2Cl_2, followed by washing with aqueous saturated NaCl. The organic layer was dried over Na_2SO_4, filtered through cotton, and concentrated *in vacuo*. The ^{1}H NMR spectrum of the residue was measured to calculate the ratio of the compounds.

Flow rate: 9.0 mL/min; concentration of TFA: 10% TFA in CH_2Cl_2; reaction time: 7.5 s; concentration of **1** 85 mM.

1,2,3,4-Tetra-*O*-acetyl-6-*O*-trityl-β-D-glucopyranoside (**1**) (250 mg, 424 □mol) was dissolved in CH_2Cl_2 (2.5 mL, 170 mM) and set in a plastic syringe. TFA (0.5 mL) was diluted with CH_2Cl_2 (2.0 mL) and set in another syringe. Each solution was flowed at 4.5 mL/min and mixed through the Y-shaped junction in the microreactor. After the solution had ran through a PTFE tube (ϕ = 2.4 mm, length = 250 mm) for 7.5 s, the solution was neutralised by aqueous saturated $NaHCO_3$, extracted with CH_2Cl_2, and dried over Na_2SO_4. The mixture was filtered, evaporated, and the ^{1}H NMR spectrum of the residue measured to calculate the ratio of the compounds. The value of the integration of peaks from 5.60 to 5.90 ppm (all H–1) was normalized as 100 for a sum of all compounds, and the integration values of 1,2,3,4-tetra-*O*-acetyl-6-*O*-trityl-β-D-glucopyranoside (**1**) (3.33 ppm, H–6a) and 1,2,3,6-tetra-*O*-acetyl-β-D-glucopyranoside (**3**) (4.53 ppm, H–6a) were used to calculate the ratio.

Yield (**2**) = (100 as the integrated value at 5.90–5.60 ppm, H–1 of **1**–**3**) – (integrated value at 3.33 ppm, H–6a of **1**) – (integrated value at 4.53 ppm, H–6a of **3**)

SUPPORTING INFORMATION

Supporting information for this article including full experimental procedures and spectral data for compounds. This material can be found via the "Supplementary Content" section of this article's webpage.

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Scheme 1. Deprotection of the trityl group of **1** in the flask.

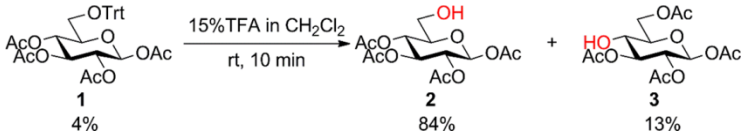

Figure 1. ^{1}H NMR spectra of (a) **1**, (b) **2**, (c) **3** for ratio calculation.

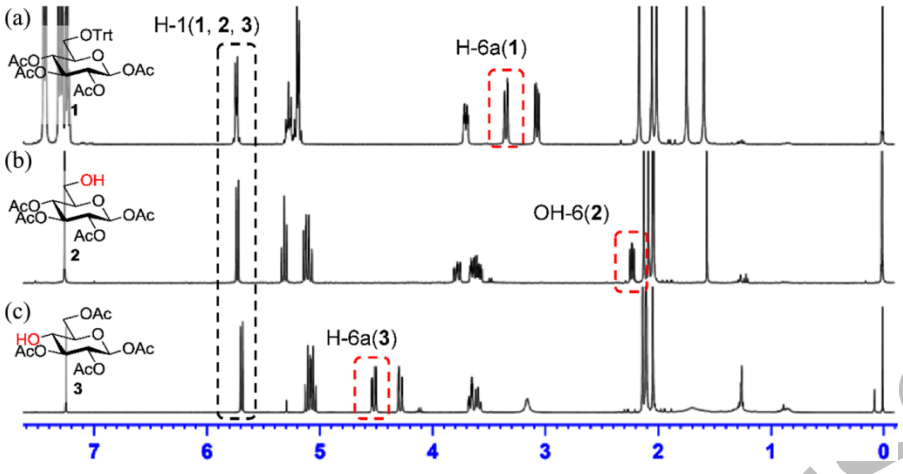

Figure 2. The microflow reaction system.

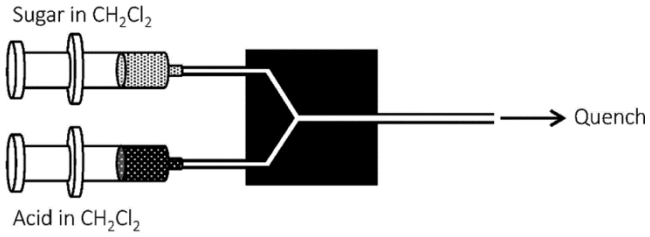

Figure 3. Optimisation of flow rate. (a) Yield of **1**, **2** and **3** at each flow rate. (b) Reproducibility of yield of **1** at each flow rate (n = 3).

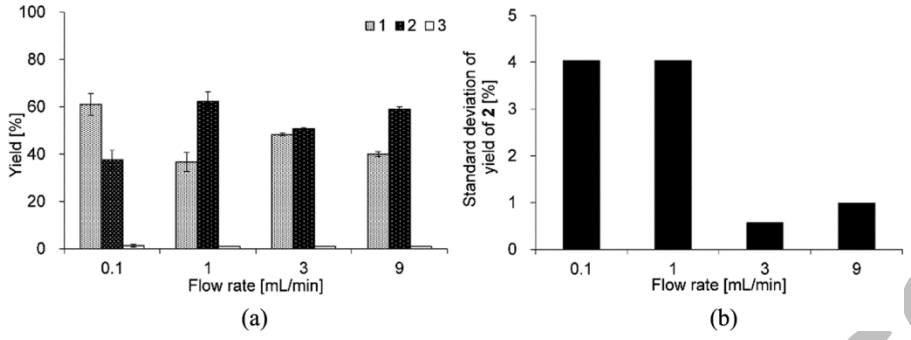

Figure 4. Optimisation of TFA concentration.

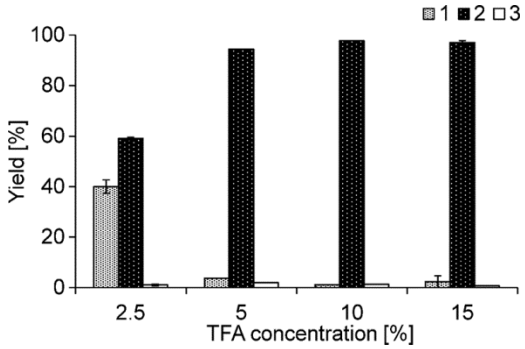

Figure 5. Optimisation of reaction time.

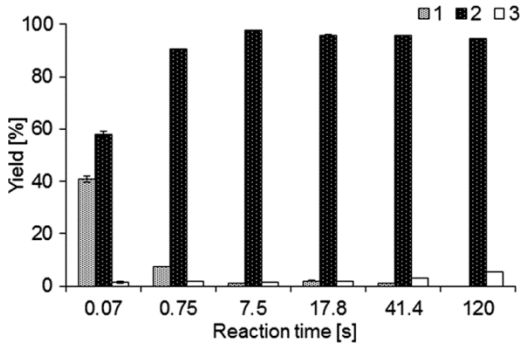

Figure 6. Optimisation of concentration of **1**.

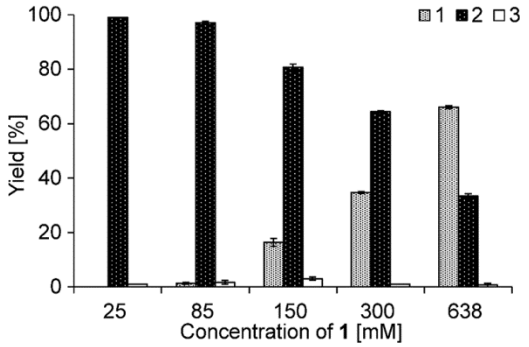

Figure 7. Other substrates for detritylation.