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Selective Monoprotection of Symmetrical Diols in a Flow Reactor

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Abstract

Desymmetrization reactions provide a powerful approach for the construction of complex molecules. Various methods have been developed for the selective monoprotection of symmetrical diols; however, their application to large-scale operations is limited. In this study, the monotetrahydropyranylation of symmetrical diols in a flow reactor has been developed, whereby the length of the flow reactor tube and the amount of acid were optimized. A higher selectivity for the monoprotected derivative was observed when the reaction was performed in a flow reactor compared with that observed in a conventional batch experiment. The efficient flow method developed herein can be applied to large-scale synthesis by numbering up the flow reactor without affecting the selectivity and yield. Since monoprotection can be achieved without using a large excess of diol, our developed flow method is effective when expensive diol must be used.

Keywords

Desymmetrization, Selective Monoprotection, Flow Synthesis, Diols, Tetrahydropyranylation

1. Introduction

Desymmetrization reactions have attracted much attention in organic synthesis because they provide a powerful tool to access complex molecules from readily available symmetrical compounds [1] [2]. For instance, the desymmetrization of diols [3] [4] [5] [6] [7], dicarbonyls [8] [9] [10] [11] [12], diamines [13], and alkenes [14] [15] [16] has been successfully applied to the synthesis of natural products such as (−)-spongidepsin [7] and merrilactone A [9] [10]. In particular, the monoprotection of diols with the tetrahydropyranyl (THP) group has been

widely used in the synthesis of bioactive compounds [17] [18] [19] [20]. However, these transformations usually result in the concomitant generation of unprotected and/or diprotected compounds in a statistical ratio. In order to overcome this limitation, the selective monoprotection of symmetrical diols has been typically performed using an excess of diol. Moreover, catalysts with a relatively small catalytic surface such as ion-exchange resins (namely, Amberlite IR-120 [21], Amberlist H-15 [22], Rellex 425 [23], Dowex 50 [24], and Nafion-H [25]), iodine [26], ZrO_2-pillared clay [27], zinc chloride [28], and aqueous acids [29] have been reported to be effective for selective monotetrahydropyranylation. However, the application of these methods to large-scale production for practical use of monoprotected diols is somewhat limited. In particular, it is very wasteful to use a large excess of expensive diol as a substrate.

In recent years, flow chemistry has emerged as an important adjunct to conventional batch chemistry [30] [31]. In a large-scale batch reactor, there is a time lag for the mixed solution to become homogeneous by stirring, which affects both the chemoselectivity and the yield of the reaction. In addition, the reaction parameters must be adapted to each scale-up condition. In contrast, flow chemistry allows for highly chemoselective reactions without side products by precisely controlling the reaction time and temperature. Moreover, flow reactions are scalable under the same conditions by simply numbering up the reactor configuration. On the basis of these advantages, we sought to investigate the selective monoprotection of diols in a flow reactor. The selective mono protection of diols using flow reactor has not been reported yet. We have previously reported the microflow synthesis of peptides using highly activated esters [32], vitamin D_3 [33], activated vitamin D_3 and its analogs [34], diamine ligands [35], and aliphatic aldehyde [36]. Herein, we report the development of a new method for selective monoprotection of diols in a flow system.

2. Materials and Methods

2.1. General

NMR spectra were recorded on a JEOL Model ECA-500 instrument, and chemical shifts were reported in parts per million (ppm) relative to internal standard (tetramethylsilane; 0.0 ppm) or solvent ($CDCl_3$; 7.26 ppm for ^1H NMR and 77.1 ppm for ^{13}C NMR) peaks. ^1H NMR spectral data were reported as chemical shift (δ, ppm), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; sp, septet; m, multiplet; br, broad), coupling constant (J, Hz), and integral value. ^{13}C NMR data were reported as chemical shift (δ, ppm) followed by multiplicity and coupling constants where applicable. All reactions were monitored by thin-layer chromatography using 0.25-mm E. Merck silica gel plates (60F-254), with visualization performed by UV light (254 nm) irradiation or staining with *p*-anisaldehyde, ceric sulfate, or 10% ethanolic phosphomolybdic acid followed by heating. Column chromatography was performed using silica gel (Chromatorex PSQ 100B, Fuji Silysia Chemical Ltd.). All reagents and chemicals were purchased

from Tokyo Chemical Industry Co., Ltd., and used as received.

2.2. General Procedure for the Monotetrahydropyranylation of Diols in a Batch Reactor

To a solution of 1,4-butanediol (**1**) (1.00 g, 11.1 mmol, 1.00 equiv.) and 3,4-dihydro-2*H*-pyran (1.20 mL, 13.3 mmol, 1.20 equiv.) in tetrahydrofuran (11.1 mL) was added 10-camphorsulfonic acid (258 mg, 1.11 mmol, 0.100 equiv.) at room temperature. After being stirred at this temperature, the reaction mixture was quenched with triethylamine and concentrated *in vacuo*. The residue was diluted with ethyl acetate and saturated aqueous $NaHCO_3$, and the organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel to give 4-((tetrahydro-2*H*-pyran-2-yl)oxy)butan-1-ol (**2**) and 1,4-bis((tetrahydro-2*H*-pyran-2-yl)oxy)butane (**3**) [21]. Unreacted **1** was found in the aqueous layer and was quantified (mmol) by the difference between the amount of starting substrate (11.1 mmol) and the amount of product (mmol).

4-((Tetrahydro-2*H*-pyran-2-yl)oxy)butan-1-ol (2)

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.60 (dd, J = 2.9, 4.0 Hz, 1H), 3.86 (ddd, J = 3.5, 8.0, 11.4 Hz, 1H), 3.80 (dt, J = 4.9, 11.4 Hz, 1H), 3.67 (brs, 2H), 3.51 (dt, J = 5.4, 10.9 Hz, 1H), 3.43 (dt, J = 5.7, 9.8 Hz, 1H), 2.19 (brs, 1H), 1.81 (m, 1H), 1.75 - 1.66 (m, 5H), 1.61 - 1.50 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 99.0, 67.6, 62.8, 62.5, 30.7, 30.2, 26.7, 25.5, 19.6.

1,4-Bis((tetrahydro-2H-pyran-2-yl)oxy)butane (3)

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.58 (dd, J = 2.9, 4.0 Hz, 2H), 3.86 (ddd, J = 3.1, 4.0, 11.2 Hz, 2H), 3.76 (m, 2H), 3.49 (m, 2H), 3.41 (m, 2H), 1.82 (m, 2H), 1.73 - 1.65 (m, 6H), 1.60 - 1.50 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 98.9, 67.4, 62.3, 30.8, 26.7, 25.6, 19.7.

2.3. Flow Reactor Setup

The flow system used in this work is shown in Figure 1. A stainless steel T-shaped

Figure 1. Flow system for tetrahydropyranylation.

mixer (inner diameter: 1.0 mm) and a Teflon® tube (inner diameter: 1.0 mm) were purchased from YMC Co. Ltd. The mixer and tube were connected with PEEK fittings, which were also purchased from YMC Co. Ltd. Solutions were introduced into the flow system using a syringe pump (Harvard PHD ULTRA) equipped with gastight syringes (SGE). The gastight syringes and Teflon® tube were connected with joints purchased from YMC Co. Ltd.

2.4. General Tetrahydropyranylation Procedure

A solution of 1,4-butanediol (**1**) (2.0 mM, 1.00 equiv.) and 3,4-dihydro-2*H*-pyran (2.4 mM, 1.20 equiv.) in tetrahydrofuran (flow rate: 0.1 mL/min) and a solution of 10-camphorsulfonic acid (X equiv.) in tetrahydrofuran (flow rate: 0.1 mL/min) were introduced into the T-shaped mixer at room temperature using the syringe pump. The resulting mixture was passed through the reaction tube (inner diameter: 1.0 mm, length: Y cm) at the same temperature. After elution for 10 min to reach a steady state, the mixture was poured into triethylamine at room temperature and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel to give 4-((tetrahydro-2*H*-pyran-2-yl)oxy)butan-1-ol (**2**) and 1,4-bis((tetrahydro-2*H*-pyran-2-yl)oxy)butane (**3**).

3. Results and Discussion

Prior to the flow experiments, tetrahydropyranylation of symmetrical diols was carried out in a batch reactor. To a solution of 1,4-butanediol (**1**) and 3,4-dihydro-2*H*-pyran (DHP) in tetrahydrofuran (THF) was added 10-camphorsulfonic acid (CSA), a commonly used Brønsted acid, at room temperature (Figure 2). Figure 3 shows the yield of diol **1** and mono- and bis-THP derivatives **2** and **3** as a function of reaction time; both **2** and **3** were gradually formed until an equilibrium mixture of **1**:**2**:**3** at a ratio of approximately 1:2:1 was reached. Good selectivity for the target product **2** was obtained for a reaction time of 6 - 10 min, although the yield was moderate.

Next, the monoprotection of **1** was performed in a flow reactor. A solution of **1**, DHP, and CSA in THF was introduced into a Teflon® tube at room temperature using a syringe pump (Table 1). The flow rate was set at 0.1 mL/min, and various tube lengths of 50, 100, 150, and 250 cm were examined, which corresponded to reaction times of 2, 4, 6, and 10 min, respectively. With a tube length of 50 and 100 cm, the mono-THP product **2** was obtained with high selectivity, although in low yields (entries 1 and 2, respectively). When a 150-cm tube was

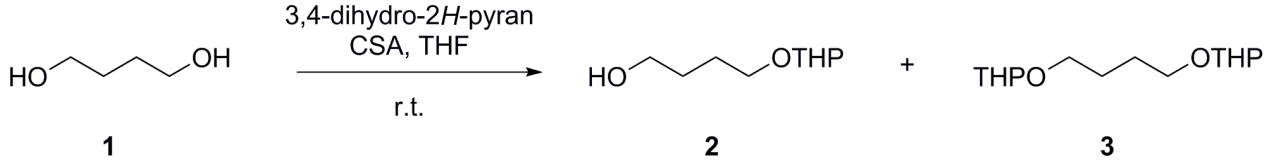


Figure 2. Tetrahydropyranylation of 1,4-butanediol (**1**) in a batch reactor.

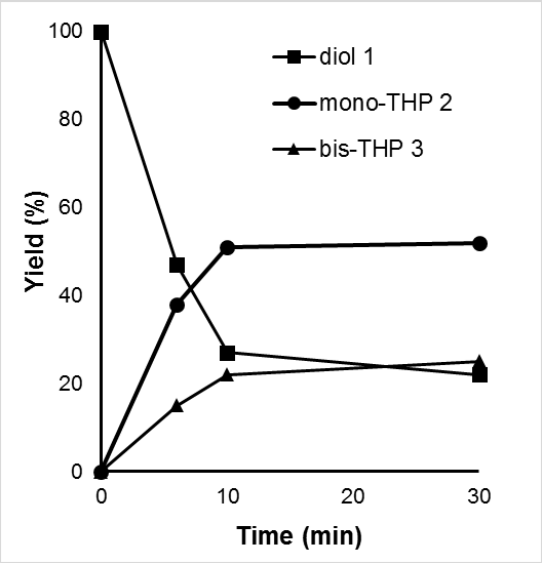
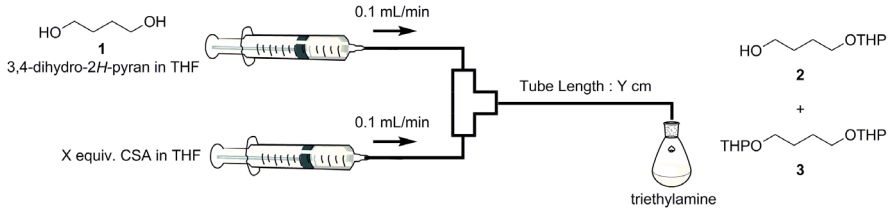


Figure 3. Yield of diol **1** and mono- and bis-THP products **2** and **3** vs reaction time. Mono- and bis-THP product **2** and **3** were isolated with column chromatography on silica gel. Unreacted **1** was quantified (mmol) by the difference between the amount of starting substrate (mmol) and the amount of product (mmol).

Table 1. Optimization of selective monotetrahydropyranylation in a flow reactor.



entry	equiv. of CSA	tube length (cm)	mono-THP product **2** (%)[a]	bis-THP product **3** (%)[a]
1	0.100	50	27	2
2	0.100	100	41	6
3	0.100	150	53	12
4	0.100	250	55	21
5	0.300	50	53	16
6	1.00	50	46	37
7	1.00	3	29	7

[a]Isolated yield.

used, the yield of the desired product **2** was improved without an appreciable reduction in selectivity (entry 3). A prolonged reaction time resulted in a decrease in selectivity and no improvement in yield (entry 4). The yield was improved when the tube was lengthened, however the byproduct of the bis-protected product also increased. Interestingly, the combination of a 50-cm tube and 0.300 equiv. of CSA (entry 5) gave almost the same result as entry 3. Moreover, shortening the tube length and increasing the amount of acid was not effective (entries 6 and 7). Hence, the flow synthesis of the mono-tetrahydropyranyl derivative required the use of a 150-cm tube and 0.100 equiv. of CSA to achieve high selectivity and sa-

tisfactory yield. It should be noted that, under all conditions tested, the starting material was not completely consumed.

4. Conclusion

In conclusion, we have developed the monotetrahydropyranylation of symmetrical diols in a flow reactor. Stirring 1,4-butanediol, DHP, and CSA in a batch reactor for 6 - 10 min resulted in the selective formation of the monoprotected diol. However, the selectivity for monotetrahydropyranylation improved when the reaction was carried out in a flow reactor. The flow method can be applied directly to large-scale synthesis by simply numbering up the flow reactor without affecting the selectivity and yield. Studies are currently underway to develop a method to remove unreacted starting diol from flow reactors.

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