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Desilylation under high pressure

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Abstract—Cleavage of *tert*-butyldiphenylsilyl (TBDPS) ether was examined under high pressure conditions (1.0 GPa) using HF/pyridine in DMF. This method proved to be exceptionally suitable for deprotecting the TBDPS group that resides at the sterically hindered position. Under these conditions, various types of other hydroxyl protecting groups (i.e. benzyl, *p*-methoxybenzyl, trityl, isopropylidene, cyclohexylidene, allyl, phthaloyl) as well as *O*- and *S*-glycosidic linkages were preserved.

In order to meet the demands that arise from synthetic studies on increasingly complex molecules, numerous types of protecting groups have been developed.[1] Among them, silyl ether based hydroxy protection is one of the most popular. Since first reported by Hanessian in 1975,[2] the *tert*-butyldiphenylsilyl (TBDPS) group has been widely used for the selective protection of primary hydroxy groups. It has also been found to be valuable for the masking of secondary alcohols, mainly due to its excellent stability under various conditions. This feature is particularly favorable in complex oligosaccharide synthesis; less hindered silyl ethers (e.g. *tert*-butyldimethylsilyl or triethylsilyl) have limited stability under typical conditions for glycosylation, deacylation, and deacetalization.

Most typically, TBDPS ethers are cleaved by a fluoride anion by taking advantage of its hard–hard interaction with silicon.[3] On the other hand, the velocity of desilylation tends to drop down markedly, as the steric hindrance increases. Forcing conditions are potentially hazardous to other sensitive functionalities. Such a situation was encountered in our synthetic study on high mannose type glycoprotein oligosaccharides. This problem was smoothly removed by performing the desilylation under high pressure, as describe below.

Compound **1** was designed and prepared as the common precursor of tertradeca- ($Glc_3Man_9GlcNAc_2$), trideca- ($Glc_2Man_9GlcNAc_2$), dodeca- ($Glc_1Man_9GlcNAc_2$) and undecasaccharide ($Man_9GlcNAc_2$), which are biosynthetic intermediates of asparagine (Asn) linked glycoproteins.[4] These oligosaccharides are attracting recent attention in connection with the glycoprotein quality control system operating in ER.[5] As the following step, liberation of the C-3 hydroxy group of Man(D_1) residue was required in order to incorporate the pendant glucose residue(s). However, seemingly straightforward transformation of **1** into **2** turned out to be challenging (Fig. 1). Treatment with Bu_4NF (TBAF)[6] gave a complex mixture and all other attempts using HF/CH_3CN,[7] HF/pyridine,[8] TASF,[9] Bu_3NHF (TBAHF),[10] and TBAF/AcOH[11] resulted in almost complete recovery of the starting material. This difficulty obviously derives from the severe steric hindrance of the TBDPS ether portion, which is sandwiched by C-2 and C-4 benzyloxy groups. To circumvent this problem, high pressure reaction conditions were applied. Since fluoridolytic desilylation presumably proceeds through the nucleophilic attack of F^- to Si, it is likely to have a negative volume

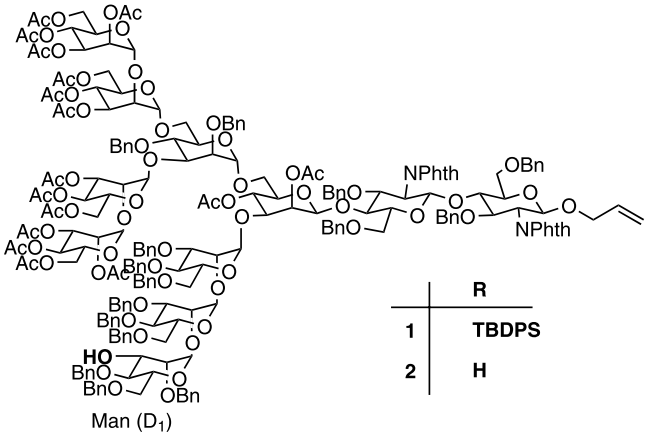

Figure 1.

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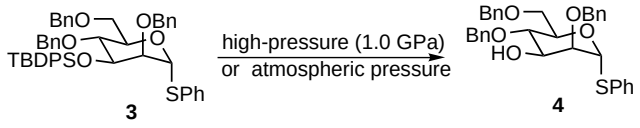
Table 1. Cleavage of TBDPS ether using fluoride reagents under high pressure conditions



Entry[a]	Reagent[b]	Time (h)	Pressure[c]	**3**/**4**[d]
1	HF/pyr	12	H	4/96
2	HF/pyr	12	A	100/0
3	HF/pyr	168	A	87/13
4	TBAHF	12	H	87/13
5	TBAHF	12	A	100/0
6	TBAHF	36	A	98/2
7	TBAF/AcOH	12	H	91/9
8	TBAF/AcOH	12	A	98/2

[a] Reaction conditions: compound **3** 0.01 mmol, reagent 100 μL, room temperature.

[b] HF/pyr: 10% HF/pyridine in DMF, TBAHF: 0.1 M tributylamine hydrofluoride in DMF, 0.1 M tetrabutylammonium fluoride and 0.3 M acetic acid in DMF.

[c] H: 1.0 GPa, A: atmospheric pressure.

[d] The ratio was determined by TLC/FID analyser.

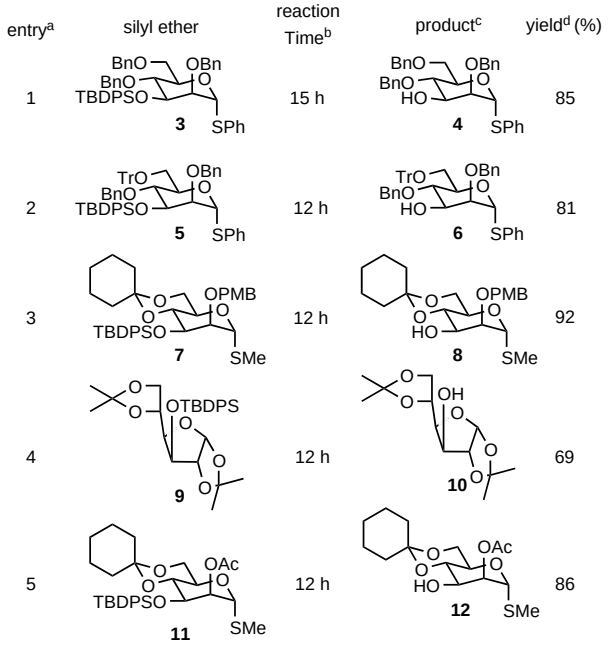
of activation ($-\Delta V^{\neq}$). Therefore, acceleration by high pressure might well be expected.[12] To our delight, treatment of 27.5 mM solution of **1** in DMF with 10% (v/v) HF/pyridine at 30°C under high pressure (1.0 GPa) for 36 h cleanly gave the desired product **2** in 86% yield. Its structure was rigorously confirmed by ^{1}H NMR and TOF mass analysis.[13]

With the above success in hand, high pressure assisted TBDPS cleavage was comparatively investigated using phenylthio 2,4,6-tri-*O*-benzyl-3-*O*-*tert*-butyldiphenylsilyl-α-D-mannoside (**3**) as a substrate and the ratio of **3** and **4** was quantified by TLC/FID (IATROSCAN) analysis. The results are summarized in Table 1. Under atmospheric pressure, desilylation with HF/pyridine (entries 2 and 3), TBAHF (entries 5 and 6), or TBAF–AcOH (entry 8) was extremely slow. On the other hand, dramatic rate acceleration was observed when HF–pyridine/DMF treatment was conducted under high pressure (entry 1), the product **4** was obtained in high yield (see Table 2, entry 1). By contrast, rate acceleration was only marginal when the reagent was replaced with either TBAHF (entry 4) or TBAF–AcOH (entry 7).

In order to ascertain that the chemoselectivity of fluoride anion-mediated desilylation was preserved under high pressure, compounds having trityl ether (**5**), *p*-methoxybenzyl ether (**7**), cyclic acetal (**7**, **9**, and **11**), and acetate (**11**) functional groups were subjected to desilylation. As summarized in Table 2, all reactions proceeded in a satisfactory manner without affecting other parts of the molecules.

On an additional note, the high pressure conditions proved to be effective, suppressing the acyl migration and applied successfully to the desilylation of trisaccharide **13**. We previously noticed that this particular

Table 2. Chemoselective cleavage of TBDPS ether

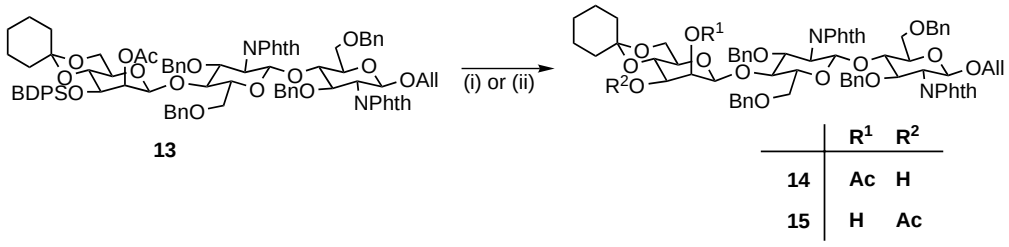


[a)] Conditions: 0.1 M solution of silylether in DMF with10% HF/pyridine at room temprature under 1.0 GPa.

[b)] The reaction was continued until TLC showed the disappearance of the starting silyl ether.

[c)] All the products were identified by ^{1}H and ^{13}C NMR spectroscopy.

[d)] Isolated yield.



Scheme 1. (i) 10% HF/Pyr in DMF, 1 GPa, **14** (88%); (ii) TBAF/AcOH in DMF, **14** (50%), **15** (32%).

transformation was problematic. Namely, while HF–pyridine gave no reaction, desilylation by TBAF/AcOH in DMF was accompanied by an extensive migration of the acetyl group to afford a mixture of 2-*O*-Ac (**14**) and 3-*O*-Ac (**15**) products. By contrast, under high pressure conditions, HF/pyridine in DMF gave compound **14** as a single product in 88% yield (Scheme 1).

In conclusion, deprotection of TBDPS ether residing at sterically hindered position was achieved using HF/pyridine in DMF under high pressure.[14] The present method may provide a rescue whenever desilylation proceeds with low reaction rate and/or is accompanied by unfavorable side reaction(s).

Acknowledgements

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13. A typical procedure: To a 1 mL Teflon reaction vessel was introduced compound **1** (96.9 mg, 0.022 mmol) dissolved in DMF (0.8 mL) containing 10% HF/pyridine (Aldrich). It was compressed to 1.0 GPa and left at 30°C for 12 h and the resulting mixture was diluted with AcOEt and washed with sat. aq. $NaHCO_3$ and brine, successively. The organic layer was dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by silica gel column chromatography (hexane–AcOEt, 10:1–1:2) to afford 78.9 mg (86%) of compound **2**; R_f 0.28 (1:1 toluene–EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 7.79–6.71 (m, Ar), 5.65–5.54 (1H, m, CH_2=C<u>H</u>), 2.10–1.88 (48H, s×14, Ac); MALDI-TOF mass: calcd for $C_{222}H_{244}N_2NaO_{74}$ $[M+Na]^+$, 4144.5. Found: 4144.2. Anal. calcd for $C_{222}H_{244}N_2O_{74}$: C, 64.65; H, 5.96; N, 0.68. Found: C, 64.44; H, 5.97; N, 0.65.
14. The RIKEN high pressure apparatus is capable of holding a 50 mL reaction volume at 2.0 GPa and scaling up to multigram should be straightforward.