Tetrahedron Letters 49 (2008) 5159–5161

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Reductive deprotection of propargyl ether by a SmI_2–amine–water system and its application to polymer-supported oligosaccharide synthesis

Shino Manabe [a,b,*], Akiharu Ueki [b], Yukishige Ito [a,*]

[a] RIKEN (The Institute of Physical and Chemical Research), Wako-shi, Saitama 351-0198, Japan
[b] PRESTO, JST, Honcho, Kawaguchi, Saitama 332-0012, Japan

ARTICLE INFO

Article history:
Received 14 May 2008
Revised 16 June 2008
Accepted 19 June 2008
Available online 22 June 2008

Keywords:
Protecting group
Deprotection reaction
Propargyl ether
SmI_2
Oligosaccharide synthesis

ABSTRACT

A SmI_2–amine–water system instantaneously deprotected aryl and alkyl propargyl ethers in a reductive manner. The utility of the propargyl group as a protecting group in oligosaccharide synthesis, and its application to polymer-supported oligosaccharide synthesis is described.

The development of protecting groups is highly desirable in synthetic organic chemistry.[1] In the field of carbohydrate chemistry, especially, the choice of protecting groups is extremely important, because it affects the reactivities and stereoselectivities of the glycosyl donor and/or acceptor.[2] Recently, the utility of propargyl ethers in carbohydrate chemistry was demonstrated in a β-mannosylation reaction, in which this protecting group was especially effective due to reduced steric buttressing.[3] The propargyl glycoside was also reported as a novel glycosyl donor activated by $AuCl_3$.[4]

To date, the use of the propargyloxy group has been relatively infrequent in organic synthesis, as well as in carbohydrate chemistry, due to the limitations of its deprotection methodology, which involves extreme reaction conditions,[5,6] exotic catalysts,[7–9] or multi-step procedures.[10]

Hilmersson's report[11] of a SmI_2–amine–water system with powerful reducing ability led us to expect this system to be useful for the deprotection of propargyl groups. Here, we report the novel, rapid, room temperature deprotection of propargyl ethers by the extremely powerful reducing combination SmI_2–amine–H_2O, and its application to polymer-supported oligosaccharide synthesis.

Initially, we investigated the effect of amine additives in the deprotection reaction of glucose-derived propargyl ether **1a** (Table 1). In the absence of amine, no reaction occurred after 1 h (entry 1). When *i*-$PrNH_2$ was used as an additive in the reaction mixture, the reaction was complete within 5 min at room temperature, and the alcohol **2** was obtained in 86% yield (entry 2). The reaction did not proceed to completion even after 1 h (entry 3) with half the amount of reductant, namely SmI_2 (5 equiv)–*i*-$PrNH_2$ (20 equiv)–H_2O (15 equiv). Et_3N (entry 4) and TMEDA (entry 5) gave satisfactory yields, but a longer reaction time was required, and some allyl ether **3a** was also obtained when TMEDA was employed as the base. Although the combination of aq 50% NaOH–SmI_2 is known to be an effective reducing reagent,[12] these conditions did not give good results in this deprotection system (entry 6). Similarly, NaSMe exhibited a slow reaction rate and low yield (entry 7).

Substituents on the propargyl termini also affected the deprotection reaction, as shown in Table 2. It is known that alkylsilyl groups and alkylgermanium groups at the alkyne termini act to protect the acidic alkyne terminus, and they are cleavable under different conditions.[13] Under our conditions, both trimethylgermanium and trimethylsilyl-substituted alkynes **1b** and **1c** gave the deprotected product **2** in 76% and 61% yield, respectively.[14,15] Unfortunately, the TIPS-substituted alkyne **1d** did not react, and the starting material was recovered. In the case of methyl-substituted alkyne **1e**, the deprotected product **2** was obtained in 30% yield together with butenyl ether **3b** (19%, 95% *E*), and 18% of the starting material **1e**.

We then investigated the applicability of this deprotection method to various propargyl ethers. Representative results are listed in Table 3, which shows that most of the propargyl ethers were cleaved within a few minutes. The acid-sensitive protecting groups MOM and acetonide were stable under these conditions

* Corresponding authors. Tel.: +81 48 467 9432; fax: +81 48 462 4680 (S.M.).
E-mail address: smanabe@riken.jp (S. Manabe).

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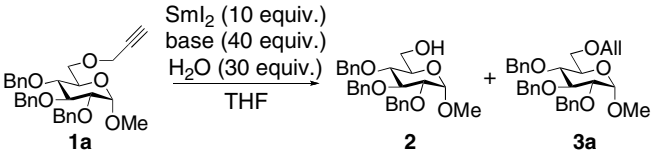
doi:10.1016/j.tetlet.2008.06.081

Table 1
The effect of base in the deprotection of propargyl ethers

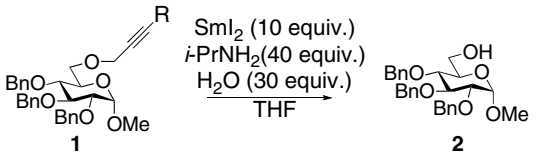


1a **2** **3a**

Entry	Base	Reaction time	Yield (%) **2**	Yield (%) **3a**
1	None	1 h	0	0
2	*i*-$PrNH_2$	15 min	86	0
3[a]	*i*-$PrNH_2$	1 h	74	11
4	Et_3N	1 h	84	0
5	TMEDA	1 h	72	16
6	50% NaOH aq	1 h	5	20
7	NaSMe	18 h	36	30

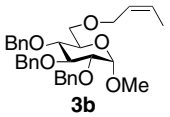
[a] SmI_2 5 equiv, *i*-$PrNH_2$ 20 equiv, H_2O 15 equiv.

Table 2
The effect of substituents on propargyl termini in propargyl ether deprotection



1 **2**

	R	Reaction time	Yield (%)
1a	H	15 min	86
1b	$GeMe_3$	1 h	76
1c	$SiMe_3$	3 h	61
1d	TIPS	16 h	0
1e	Me	10.5 h	30



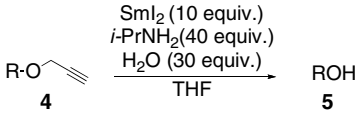
3b

(entries 2 and 3). After deprotection of the propargyl ether, **4d** and **4e** were obtained as single diastereomers. Racemization at the chiral centers was negligible. The deprotection yield of **4d** was not satisfactory, and the corresponding allyl ether was obtained in 30% yield (entry 4). Phenolic propargyl ethers were also deprotected in good yields (entries 6 and 7). Unfortunately, the acetamide-containing substrate **4g** gave a low yield, because reduction to the methylamine occurred as a competitive reaction.

This methodology was next applied to oligosaccharide synthesis (Scheme 1). The acceptor **7** was glycosylated with propargyl ether carrying thioglycoside **6** under NIS–TfOH activation conditions. The glycosylation reaction proceeded cleanly in quantitative yield with a 3:2 α:β ratio, and the propargyl group was not susceptible to I_2 addition, unlike the allyl group. After separation of the anomeric stereoisomer, the propargyl group of the β isomer **8b** was deprotected in 79% yield. These results demonstrated the utility of propargyl ether as a protecting group in oligosaccharide synthesis.

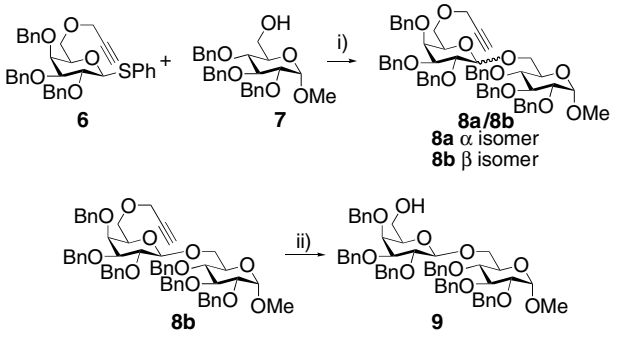
Finally, this methodology was applied to polymer-supported oligosaccharide synthesis.[15] The propargyl ether carrying galactose thioglycoside **10** was attached to a Wang linker via glycosylation in quantitative yield (2:1 α:β). After removal of the acetyl group, the resulting phenoxide was immobilized to bromo poly(ethylene glycol) methyl ether (average M.W. 750) in the presence of Cs_2CO_3. As we previously reported,[15a–e] PEG's high polarity enabled purification of the PEGylated sugar by passing it through a silica gel pad.

Table 3
The deprotection of propargyl ethers in various substrates



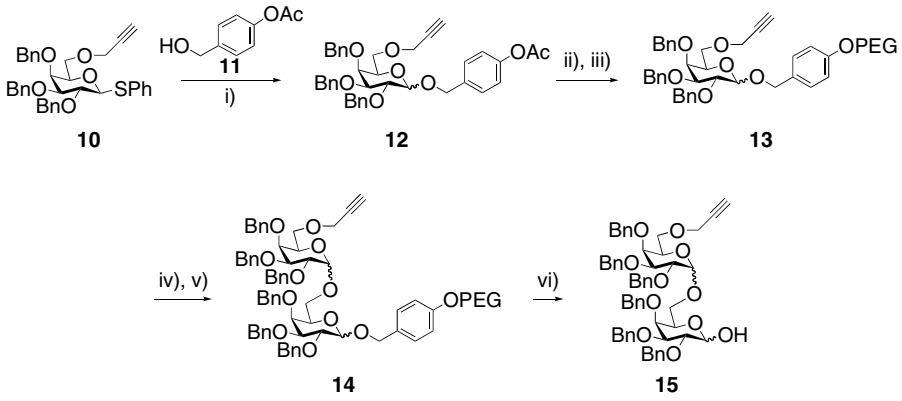
4 **5**

Entry	R-O	Time	Yield (%)
1	Ph, O **4a**	5 min	92
2	O, O, O **4b**	5 min	70
3	MOMO, O, OTBDPS **4c**	10 min	93
4	O **4d**	1 h	43
5	tBu, O **4e**	15 min	89
6	O, OTBS **4f**	5 min	79
7	O, NHAc **4g**	15 min	68



6 **7** **8a/8b**
8a α isomer
8b β isomer
8b **9**

Scheme 1. Glycosylation reaction and deprotection of propargyl-ether-carrying sugar. Reagents and conditions: (i) NIS, TfOH, CH_2Cl_2, −40 °C, 15 min, quant., **8a**:**8b** 3:2; (ii) SmI_2, *i*-$PrNH_2$, H_2O, THF, rt, 10 min, 79%.



Scheme 2. Polymer-supported disaccharide synthesis. Reagents and conditions: (i) NIS, TfOH, CH_2Cl_2, −40 °C, 30 min, quant.; (ii) NaOMe, MeOH, rt, 2 h, 93%; (iii) MPEG-Br, Cs_2CO_3, CH_3CN, 14 h, 80 °C, 92%; (iv) SmI_2, *i*-$PrNH_2$, H_2O, THF, rt, 15 min, 63%; (v) **6**, NIS, TfOH, CH_2Cl_2, −40 °C, 8 h, 94%; (vi) TFA:CH_2Cl_2 1:4, rt, 1 h, 64%.

Again, the propargyl group was deprotected by the SmI_2–*i*-$PrNH_2$–H_2O system within 15 min in 63% yield. Glycosylation with **10** was carried out and the disaccharide **15** (newly formed glycosyl bond, α:β 1:1) was obtained in 64% yield after cleavage from PEG (Scheme 2).

Although the mechanism of this reaction is not yet clear,[16] a novel methodology for the rapid reductive deprotection of propargyl groups has been developed. The methodology was found to be useful in the construction of simple molecules as well as in oligosaccharide synthesis. Our method was effective for both alkyl and aryl propargyl groups, and was operationally simple.

General procedure for deprotection of propargyl ether: Freshly prepared SmI_2 solution[17] (ca. 0.1 M THF solution, 10 equiv) was added to a mixture of propargyl ether (1 equiv) and *i*-$PrNH_2$ (40 equiv). Commercially available SmI_2 could also be used. H_2O (30 equiv) was added dropwise at room temperature under Ar atmosphere. The mixture was stirred and the reaction progress was monitored by TLC at room temperature. After the reaction was completed, the mixture was quenched with 10% aq citric acid. The aqueous layer was extracted with $CHCl_3$. The combined layers were washed with water and brine. After drying the extract over $MgSO_4$, the solvent was evaporated. The residue was purified by silica gel column chromatography.

Acknowledgments

We thank Ms. A. Takahashi for her technical assistance. S.M. thanks the JSPS for a Grant-in Aid for Scientific Research (C) (Grant No. 19590032).

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