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Propargyloxycarbonyl (Poc) as a Protective Group for the Hydroxyl Function in Carbohydrate Synthesis

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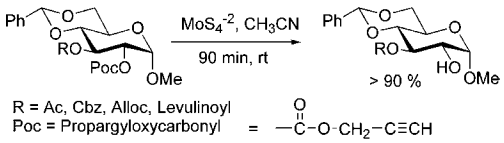
ABSTRACT



The propargyloxycarbonyl (Poc) group can be used for the selective protection of the hydroxyl function in carbohydrates and can be removed under neutral conditions using tetrathiomolybdate MoS_4^{2-} (1) in CH_3CN at room temperature. Under the conditions of deprotection benzylidine acetals, benzyl ethers, acetyl and levulinoyl esters, and allyl and benzyl carbonates are left untouched. It has also been shown that the new protective group (Poc) is compatible with acidic, basic, and also glycosylation conditions.

Many of the steps required in carbohydrate synthesis involve selective protection and deprotection of hydroxyl groups. In contrast with peptide synthesis, generalized methods cannot be applied to oligosaccharide formation. The development of solid-phase synthesis of oligosaccharides[1] has been hampered by the lack of effective differential protection/deprotection strategies. In addition, problems are still encountered in achieving high yielding and stereoselective couplings for multifunctional carbohydrate donors and acceptors.[2] In this context, new protection/deprotection methods will play an important role in carbohydrate chemistry.

The propargyloxycarbonyl (Poc**)** protecting group, which has been developed in our laboratory, has served as an efficient protective group for amines,[3] as chemoselective deprotection under neutral conditions using benzyltriethylammonium tetrathiomolybdate, $[PhCH_2NEt_3]_2MoS_4$ (**1**), can be achieved. Moreover, Poc is stable under acidic and mild basic conditions and the deprotected products can be isolated by simple filtration.

In this letter we describe the first systematic study of the application of Poc as a protecting group for the hydroxyl function in carbohydrates.

The regioselective introduction of Poc group at the C-2 position of methyl-4,6-*O*-benzylidene-α-D-glucopyranoside **3** has been achieved using TMEDA as a base at −78 °C in CH_2Cl_2.[4] Using this methodology methyl-2-*O*-propargyloxycarbonyl-4,6-*O*-benzylidene-α-D-glucopyranoside **4** was synthesized in 80% yield with none of the 3-O-protected derivative. The only byproduct was the doubly protected compound **5**. On the other hand, reaction of methyl-4,6-*O*-(*p*-methoxybenzylidene)-*β*-D-glucopyranoside **7**[5] with Poc-Cl using TMEDA as a base at −78 °C in CH_2Cl_2 gave selectively the 3-hydroxy Poc-protected compound **8** in 75% and doubly protected compound **9** in 20% yield, respectively. In addition, selective protection of the 6-OH of methyl-2,3-di-*O*-benzyl-α-D-glucopyranoside **10** with Poc-Cl was achieved

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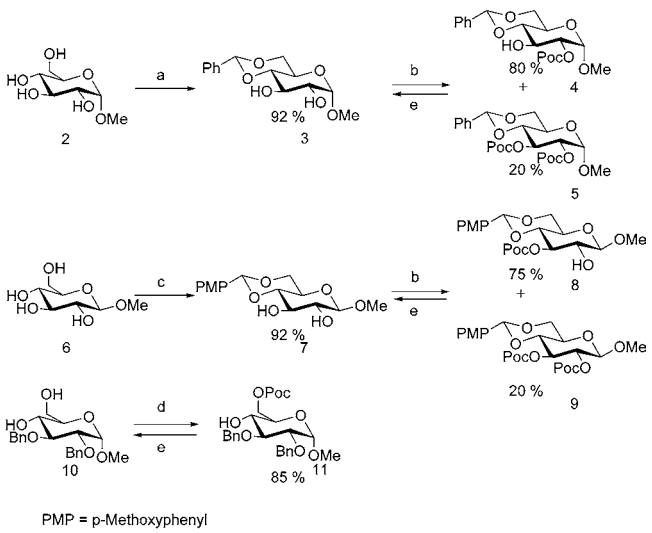
Scheme 1. Selective Protection and Deprotection of the Poc Group[a]

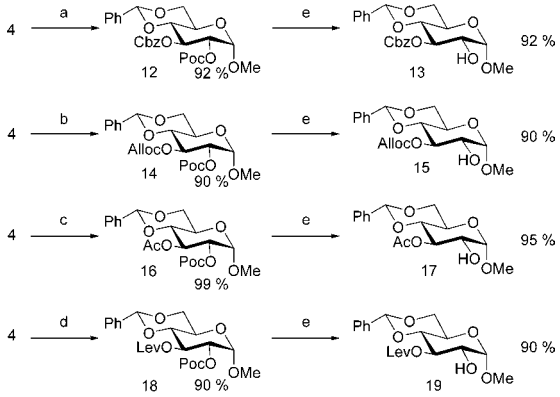


[a] (a) $PhCH(OMe)_2$, *p*-Ts-OH·H_2O, DMF. (b) Poc-Cl, TMEDA, CH_2Cl_2, −78 °C. (c) *p*-$MeOC_6H_4(OMe)_2$, *p*-TsOH·H_2O, DMF. (d) Poc-Cl, TMEDA, CH_2Cl_2, −20 °C. (e) MoS_4^{2-}, CH_3CN, 28 °C.

to give **11** in 85% yield (Scheme 1). Treatment of **4**, **5**, **8**, **9**, and **11** with MoS_4^{2-} (**1**) gave the corresponding deprotected products **3**, **7**, and **10**, respectively, in excellent yield. These results indicated that the benzylidine, *p*-methoxybenzylidineacetals, and benzyl protecting groups are stable under the conditions of deprotection.

The 3-hydroxy function of compound **4** was protected with different protective groups that are widely applied in carbohydrate chemistry. The benzyloxycarbonyl (Cbz) is generally used as protecting group for amines[6] in peptide synthesis and for hydroxyl function in carbohydrate synthesis.[7] Reaction of **4** with benzyloxycarbonyl chloride (Cbz-Cl) gave compound **12** in 92% yield. Treatment of **12** with tetrathiomolybdate **1** gave chemoselectively Poc-deprotected compound **13** in 92% yield. The allyloxycarbonyl (Alloc) has also been used as protecting group for alcohols[8] in carbohydrate chemistry,[8] as well as for amines in oligosacharide,[10] peptide,[11] and solid-phase oligonucleotide synthesis.[12] Treatment of **4** with allyloxycarbonyl chloride (Alloc-Cl) in the presence of TMEDA in CH_2Cl_2 furnished **14**. Our chemoselective deprotection methodology also proved effective for the cleavage of the 2-*O*-Poc group in the presence of 3-*O*-Alloc to form **15** in excellent yield (90%). Treatment of **4** with acetic anhydride in pyridine gave acetate **16**. Selective deprotection of 2-*O*-Poc in the presence of acetyl ester has been achieved within 90 min to give **17** in 95% yield. Levulinate esters have been used as one of the orthogonal protecting groups in the presence of *p*-methoxybenzyl (PMB), tertiarybutyldiphenylsilyl (TBDPS), and chloroacetyl (ClAc) function in oligosaccharide libraries synthesis.[13] Treatment of **4** with levulinic acid in the presence of DCC, DMAP in CH_2Cl_2 gave **18**. In this case also Poc group has been deprotected in the presence of levulinoyl ester to give **19** in 90% yield (Scheme 2).

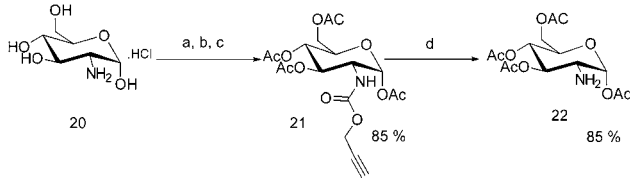
Scheme 2. Chemoselective Deprotection of **Poc** Using MoS_4^{2-} (**1**)[a]



[a] (a) Cbz-Cl, TMEDA, CH_2Cl_2, 0 °C. (b) Alloc-Cl, TMEDA, CH_2Cl_2, 0 °C. (c) $(CH_3CO)_2O$, DMAP, pyridine. (d) Levulinic acid, DCC, DMAP, CH_2Cl_2. (e) MoS_4^{2-}, CH_3CN, 28 °C.

We also used the Poc protecting group in the case of glucosamine **20**.[14] The Poc-protected glucopyranose derivative **21** on treatment with tetrathiomolybdate **1** yielded the free amine **22** (85%) (Scheme 3).

Scheme 3[a]



[a] (a) NaOMe, MeOH. (b) Poc-Cl, Et_3N. (c) Ac_2O, pyridine. (d) MoS_4^{2-}, CH_3CN, 28 °C.

After optimizing the conditions for chemoselective deprotection of Poc, we focused our attention on the formation of

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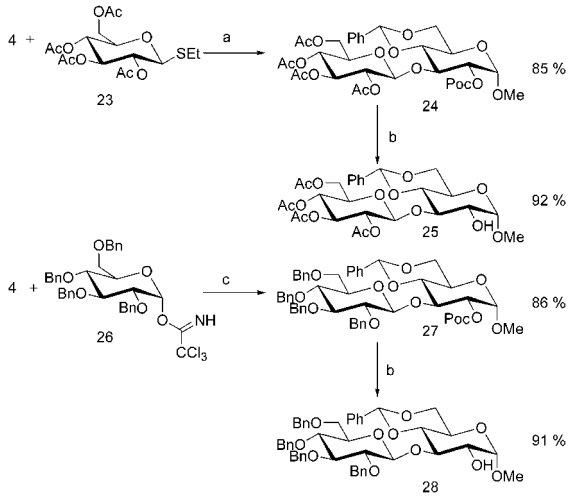
Scheme 4[a]



[a] (a) NIS, TMSOTf, CH_2Cl_2, 4 Å MS, 0 °C. (b) MoS_4^{2-}, CH_3CN, 28 °C. (c) TMSOTf, CH_2Cl_2, 4 Å MS, 0 °C.

disaccharides where Poc-protected carbohydrate derivatives can be used as glycosyl acceptors.

We examined two typical glycosylation conditions that are widely used in oligosaccharide synthesis. The reaction of methyl glycoside **4** with thioglycoside **23** under Fraser-Reid conditions[15] (NIS/cat. TMSOTf) furnished compound **24** in 85% yield. Similarly the reaction of **4** with trichloroacetimidate **26**[16a] under Schmidt conditions[16] gave the disaccharide **27** in 86% yield. These experimental results indicate that the Poc protective group could withstand Lewis acidic conditions and also olefin reactive reagents such as NBS and NIS, whereas allyloxycarbonyl (Alloc) is not compatible.[9] Treatment of **24** and **27** with tetrathiomolybdate **1** in CH_3CN at room temperature gave Poc-deprotected products **25** and **28**[17] in 92% and 91% yield, respectively (Scheme 4).

In conclusion, we have demonstrated that the Poc group can be used effectively for orthogonal protection of hydroxyl groups in carbohydrates and can be selectively deprotected with tetrathiomolybdate **1**. It has also been shown that the Poc group is stable[18] to a variety of glycosylation conditions for use in oligosaccharide synthesis.

General Procedure for Poc-Protected Carbohydrate Derivatives. Synthesis of 6-O-Proporgyloxycarbonyl-α-D-methyl-4,6-di-*O*-benzyl-glucopyranoside (11). To a cooled (−60 °C) and stirred solution of compound **10** (0.20 g, 0.53 mmol) and TMEDA (53 μL, 0.32 mmol) in dichloromethane (10 mL) was added dropwise propargyloxycarbonyl chloride (70 μL, 0.58 mmol), and the mixture was stirred at −60 °C for 0.5 h. TLC analysis (ethyl acetate/petroleum ether, 1:2 v/v) indicated the completion of the reaction. The mixture was diluted with dichloromethane (20 mL) and washed with water (10 mL) and brine (10 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel to give **11** (0.199 g, 85%) as a colorless gum. IR (thin film): 3490, 3285, 2126, 1753, cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.32−7.35 (m, 10H, phenyl), 5.03 (d, J = 11.7 Hz), 4.60−4.79 (m, 6H), 4.38 (bs, 1H), 3.78 (t, J = 9.3 Hz), 3.34−3.53 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.6, 138.6, 137.8, 128.5, 128.4, 127.9, 127.9, 127.8, 127.7, 98.0, 81.0, 79.5, 76.8, 75.7, 75.3, 73.0, 69.6, 68.9, 67.0, 55.3, 55.2. Low resolution MS: m/z 456 (M^+). Anal. calcd for $C_{25}H_{28}O_8$: C, 65.78; H, 6.18. Found: C, 65.43; H, 6.19.

General Procedure for the Deprotection of Poc with Tetrathiomolybdate 1. Deprotection of 11. To a well-stirred solution of **11** (0.456 g, 1 mmol) in CH_3CN (10 mL) was added tetrathiomolybdate **1** (0.670 g, 1.1 mmol) all at once. The reaction mixture was stirred for 3 h at room temperature (28 °C). The solvent was removed under reduced pressure, and the black residue was extracted with dichloromethane/diethyl ether (1:1, 10 mL × 3) and filtered through a Celite pad. The filtrate was concentrated, and the residue was purified by chromatography on silicagel using ethyl acetate to get compound **10** (0.355 g, 95%) as a solid, mp 79 °C, lit.[19] 79−80 °C.

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Supporting Information Available: ^1H and ^{13}C spectra of compounds **4**, **5**, **8**, **9**, **11**−**19**, **24**, **25**, **27**. This material is available free of charge via the Internet at http://pubs.acs.org.

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