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USE OF (PHENYLDIMETHYLSILYL)METHOXYMETHYL AND (PHENYLDIMETHYLSILYL)METHYL ETHERS AS PROTECTING GROUPS FOR SUGAR HYDROXYLS*

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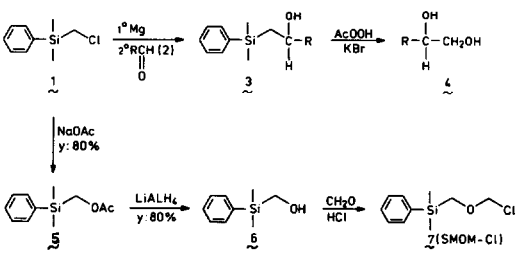
ABSTRACT: The reagent (phenyldimethylsilyl)methoxymethyl chloride (SMOM-Cl) proved to be very convenient for the formation of the corresponding SMOM ethers of primary and secondary hydroxyls of sugars. Further, (phenyldimethylsilyl)methanol (SMOH), the precursor of SMOM-Cl, could be used for the protection of the anomeric centre with the SM group. Both protecting groups can be removed smoothly by oxidation with KBr/AcOOH, and are compatible with protecting group manipulations in sugar chemistry.

In earlier studies[1] from this laboratory we reported that the phenyldimethylsilyl function could serve as a masked form of the hydroxy group at C-7 in the synthesis of L-*glycero*-α-D-*manno*-heptopyranoside containing saccharides. Thus reaction (see Scheme 1) of the Grignard reagent, derived from **1** and magnesium, with the aldehyde **2** (*i.e.*, a properly

Scheme 1 (y=yield)



protected alkyl-α-D-*manno*-hexodialdo-1,5-pyranoside) afforded in very good diastereomeric purity the corresponding phenyldimethylsilyl derivative **3**. Unmasking of the $PhMe_2Si$ moiety could then be effected with KBr and AcOOH to give the diol derivative **4**. The latter features, together with the finding[1c] that the $PhMe_2Si$ group in **3** was also compatible with glycoside coupling procedures involving several halophilic promotors [*e.g.*, silver triflate, trimethylsilyl triflate], urged us to investigate the feasibility of applying the (phenyldimethylsilyl)methoxymethyl (SMOM) ether as a protecting group for hydroxyl functions.

We herein report that the SMOM group and its precursor phenyldimethylsilylmethanol [*i.e.* **6** (SMOH) in Scheme 1] can be used successfully for the protection of hydroxyls and the anomeric centre of sugars, respectively.

For the introduction of the SMOM group we prepared the SMOM chloride **7**. The individual steps in the synthesis of **7** are illustrated in Scheme 1. Thus treatment of commercially available **1** with sodium acetate and subsequent reduction of the acetate **5** with $LiAlH_4$,according to Ambasht *et al.*[2], afforded homogeneous **6** in an overall yield of 64%. The conversion of **6** into **7** was easily executed by the same procedure reported by Corey *et al.*[4] for the synthesis of MEM-Cl. The crude chloride **7** thus isolated was used without further purification[5].

The protection of the primary hydroxyl of the partially benzylated methyl-α-D-mannopyranoside **8** (see Scheme 2) with the SMOM group was performed as follows. To a solution of **8** (1 mmol) in acetonitrile (5 ml) was added N,N-diisopropylethylamine (DIPEA, 5 eq.) and **7** (3 eq.). T.l.c.-analysis, after 3 h at 40°C, showed complete conversion of **8** into a product with a higher R_f-value. Workup and purification (silica gel) afforded homogeneous **9**[6] in an excellent yield. Cleavage of the SMOM group from **9** with peroxyacetic acid and potassium bromide in acetic acid/sodium acetate for

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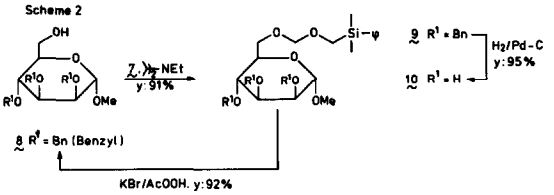
This paper is dedicated to Professor C.B. Reese on the occasion of his 60th birthday.

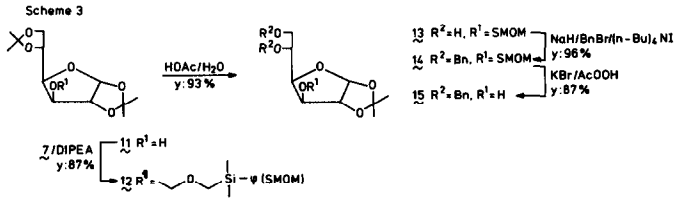
Scheme 2



1.5 h at 20°C afforded solely **8**. On the other hand, removal of the benzyl groups from **9** by hydrogenolysis gave the debenzylated derivative **10**. It was also established that the SMOM group in **9** survived prolonged exposure (15 h at 20°C) to excess $(n\text{-Bu})_4NF$ in dioxane as well as basic treatment (*i.e.*, NaOMe/MeOH and 4 N NaOH/dioxane/methanol) during 8 h at 20°C. In both cases **9** could be recovered in a nearly quantitative yield.

Reaction of the secondary hydroxyl of the diacetonide derivative **11** (Scheme 3) with **7** and DIPEA for 4 h at 20°C

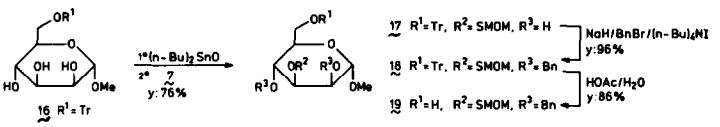
Scheme 3



afforded, after usual workup and purification, compound **12**. Acidolysis of the 5,6-O-isopropylidene function in **12** gave **13**, the diol system of which was benzylated, in the presence of $(n\text{-Bu})_4NI$[7], resulting in the isolation of **14**. Removal of the SMOM group from **14**, as mentioned before (*i.e.*, **9** → **8** in Scheme 2), yielded **15** in an excellent yield.

The compatibility of the SMOM group with the conditions used for regioselective benzylation is illustrated in Scheme 4. For example, reaction of **7** (1.5 eq.) for 3 h at 35°C with the stannylene complex of **16**, prepared[8] by refluxing **16**

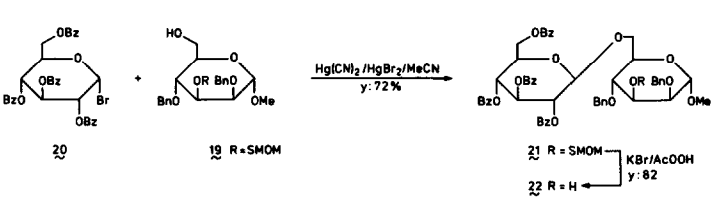
Scheme 4



with dibutyltin oxide in methanol, yielded the 3-O-SMOM-D-mannopyranoside derivative **17**. Benzylation of **17**, and subsequent acidic hydrolysis of the trityl (Tr) group from **18**, afforded **19** in an overall yield of 82%.

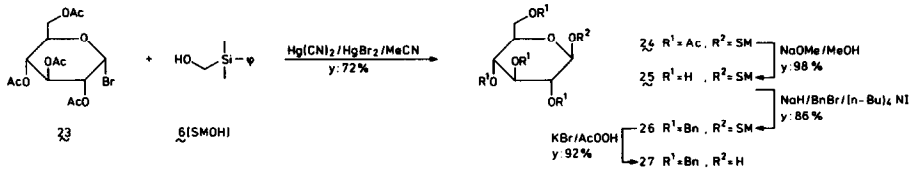
The stability of the SMOM group towards a halophilic promotor mediated glycosidation is exemplified in Scheme 5. Condensation of the benzoylated glycosyl donor **20** with acceptor **19**, under Helferich conditions[9], gave the β-linked disaccharide **21**, which was smoothly converted, after oxidative removal of the SMOM group, into the valuable disaccharide **22**.

Scheme 5



The use of (phenyldimethylsilyl)methanol **6** as a protecting group of an anomeric hydroxyl is illustrated in Scheme 6.

Scheme 6



Helferich promoted glycosidation of **23** with a slight excess of **6** afforded the β-D-glucopyranoside **24** in an excellent yield. Zemplén deacetylation of **24**, followed by benzylation of **25**, gave **26** in an overall yield of 82%. Finally, removal of the (phenyldimethylsilyl)methyl group (SM group) from **26** to afford **27** (mixture of anomers) was easily accomplished within 1.5 h at 20°C using the same reagents as applied before for the deblocking of the SMOM group. Apart from this, it is also of interest to note that the SM-group was not affected by fluoride-ion. Thus treatment (18 h at 20°C) of **26** with an excess of $(n\text{-}Bu)_4NF$ in dioxane led to the quantitative recovery of the starting compound.

In conclusion, the results presented herein indicate that the SMOM and SM protecting groups are compatible with the commonly used protecting group manipulations and glycosidation protocols[10] in sugar chemistry. We firmly believe that the favourable features of the above described new protecting groups will be of great value towards the synthesis of complex oligosaccharides.

ACKNOWLEDGEMENT

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3. Compound **6** was purified by distillation (b.p. 125°C, 20 mm Hg). Relevant ^1H and ^{13}C NMR data (δ-values) are as follows. ^1H NMR ($CDCl_3$): 7.38-7.02 (m, 5H, Ph), 3.15 (s, 2H, CH_2), 0.10 (s, 6H, Me_2Si). ^{13}C NMR ($CDCl_3$): 133:7, 129.2, 127.8 (C, Ph), 55.1 (CH_2-Si), - 5.0 (CH_3, Me_2Si).

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5. Crude **7** thus obtained proved to be pure for more than 90% as gauged by IR, ^1H and ^{13}C NMR spectroscopy.

6. Satisfactory elemental analysis data were obtained for compounds **9**, **10**, **12**, **15**, **17**, **21**, **22** and **24**. Relevant ^1H NMR ($CDCl_3$) data (δ-values) of compounds: **9**, 4.78 (1H, d, H-1, $J_{1,2}$= 2.0 Hz), 4.61 (1H, s, O-CH_2-O), 3.33 (2H, s, Si-CH_2), 0.39 (6H, s, (Me_2Si); **10**, 4.64 (2H, s, O-CH_2-O), 4.62 (1H, d, H-1, $J_{1,2}$= 1.7 Hz), 3.40 (2H, d, Si-CH_2), 0.30 (6H, s, Si-(Me_2Si); **12**, 5.82 (1H,d, H-1, $J_{1,2}$= 2.5 Hz), 4.72 (2H, s, O-CH_2-O), 3.45 (2H, AB, Si-CH_2), 0.35, 0.34 (6H, 2xs, (Me_2Si); **13**, 5.86 (1H, d, H-1, $J_{1,2}$= 3.5 Hz), 4.71 (2H, AB, O-CH_2-O), 3.42 (2H, AB, CH_2-Si), 0.36 (6H, s, (Me_2Si); **17**, 4.73 (2H, s, O-CH_2-O), 4.7- (1H, d, H-1, $J_{1,2}$= 1.5 Hz), 3.41 (2H, O-CH_2O), 0.33 (6H, s, (Me_2Si); **21**, 4.92 (1H, d, H-1, $J_{1,2}$= 8.5 Hz), 4,72 (1H, s, O-CH_2O), 4.62 (1H, d, H-1, $J_{1,2}$= 1.5 Hz), 3.43 (2H, AB, CH_2-Si), 0.33 (6H, s, (Me_2Si); **22**, 4.91 (1H, d, H-1, $J_{1,2}$= 8.5 Hz), 4.63 (1H, d, H-1, $J_{1,2}$= 1.5 Hz); **24**, 4.37 (1H, d, H-1, $J_{1,2}$= 8.1 Hz), 3.85, 3.27 (2H, 2d, CH_2Si), 0.32, 0.30 (6H, 2xs, (Me_2Si).
Relevant ^{13}C NMR ($CDCl_3$) data (δ-values) of compounds: **9**, 98.7 (C-1), 98.1 (O-CH_2-O), 59.4 (CH_2-Si), - 4,7 (Me_2Si); **10**, 99.3 (C-1), 99.2 (O-CH_2-O), 60.6 (CH_2-Si), - 4.2 (Me_2Si); **12**, 105.0 (C-1), 97.1 (O-CH_2O), 60.3 (CH_2-

Si), 26.6, 26.0, 25.2. (4 x CH_3, isoprop.), - 4.6 (Me_2Si); **13**, 104.9 (C-1), 98.7 (O-CH_2-O), 60.9 (CH_2-Si), 26.6, 26.0 (CH_3, isoprop.), - 4.6 (Me_2Si); **14**, 104.9 (C-1), 99.5 (O-CH_2-O), 73.3, 72.2 (2 x CH_2Bn), 61.0 (CH_2-Si), - 4.5 (Me_2Si); **17**, 100.2 (C-1), 98.7 (O-CH_2-O), 61.1 (CH_2-Si), - 4.7 (Me_2Si); **18**, 98.1 C-1), 97.6 (O-CH_2-O), 72.2, 72.0 (2 x CH_2, Bn), 62.6 (CH_2Si) - 4.8 (Me_2Si); **19**, 99.0 (C-1), 97.8 (O-CH_2-O), 60.1 (CH_2-Si), - 4.5, - 4.6 (Me_2Si); **21**, 101.5 (C-1), 98.2 (C-1), 97.4 (O-CH_2-O), 59.9 (CH_2-Si), - 4.6, - 4.7(Me_2Si); **22**, 101.8 (C-1), 97.5 (C-1).

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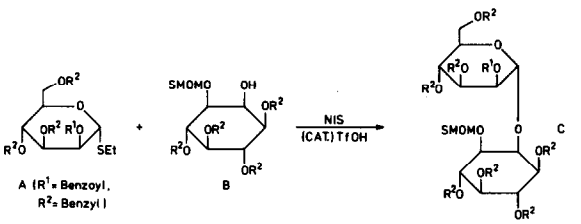
10. Preliminary experiments indicated that the SMOM group also survived the recently developed by us (G.H. Veeneman *et al.*, Tetrahedron Lett. in press) N-iodosuccinimide (NIS)/trifluoromethanesulfonic acid (TfOH: catalytic amount) mediated coupling of thioglycoside A with the axially orientated hydroxyl group of the DL-*myo*-inositol derivative B to give the α-linked product C in a yield of 70%.



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