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Simple formylacetal (CH_2) as a novel linker for saccharide synthesis on soluble-polymer support

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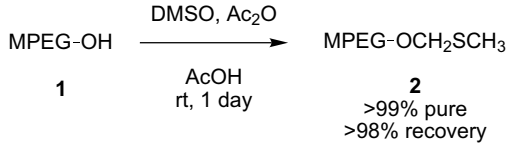
Abstract—Described herein is a new formylacetal (CH_2) linker for immobilization of small molecules onto a soluble-polymer support, poly(ethylene glycol) ω-monomethyl ether (MPEG), and its application to saccharide synthesis. This small linker allows immobilization of a hindered hydroxy group such as the 4-hydroxy group of glucose onto MPEG. The linker is stable under several reaction conditions including glycosylation. Removal of this support was found to be achieved through cleavage of the CH_2 linker either by a Lewis acid (TMSI or $Ce(OTf)_x$) or a Brønsted acid (trifluoroacetic acid) in moderate to good yields. In combination with solid acid catalyst, simpler operations became possible during the working-up and purification processes.

Since its introduction into the field of synthetic organic chemistry,[1] polyethylene glycol (PEG) has been recognized as a convenient soluble polymer to raise the efficiency in synthetic works.[2] The significant feature of this support is that it easily precipitates from diethyl ether. Because a small molecule that attaches to PEG readily precipitates upon addition of diethyl ether as well, this technique has been used for rapid and diverse synthesis of small molecules. Several types of linkers have been reported so far to attach small molecules to PEG; succinate ester,[3] *p*-alkoxybenzyl ether,[4] arylsulfonamide,[5] dioxyxylyl diether (DOX),[6,7] and alkyl silyl ether.[8] As a part of our ongoing programs directed toward construction of small-molecule libraries used for chemical genetics studies, we have developed a new formylacetal (CH_2) linker, which can trap and release small molecules both in good yield. Protocols for these transformations and their application for carbohydrate chemistry are described herein.[9]

We used poly(ethylene glycol) ω-monomethyl ether (MPEG-OH **1**, av MW 5000) in the present study. Since formylacetal linkage is known to be formed from (methylthio)methyl (MTM) ether,[10] introduction of this functionality to MPEG-OH **1** was investigated. Conversion of commercially available MPEG-OH **1** into its MTM ether **2** under standard conditions (MTMCl, NaH, NaI, THF, rt) was first attempted. The reaction was roughly monitored by the MALDI-TOF mass spectrum of the mixture, and the conversion yield after 3 days was calculated to be 51% from the ^1H NMR spectrum, but the reaction never reached completion even by warming up to 50 °C for 3 days.[11] We then tried the reaction by DMSO and Ac_2O.[12] The reaction proceeded quite smoothly to give the desired MTM ether **2** in a quantitative conversion after 1 day (Scheme 1). No trace of an oxidized product was detected. According to the procedure reported by Krepinsky and co-workers,[6] **2** was isolated by simple precipitation from diethyl ether.[13]

With MPEG-OMTM **2** in hand, we then investigated efficient reaction conditions to couple with a glucose



Scheme 1.

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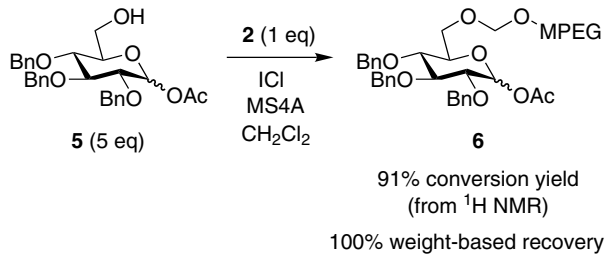
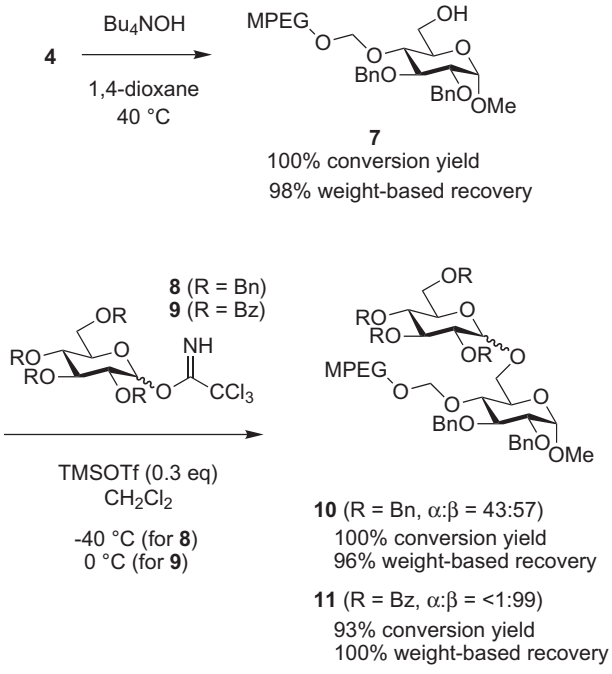
derivative **3**, which was prepared in four steps and has a hindered, secondary hydroxy group. The reaction was carried out with 10 equiv of **3** in the presence of MS4A in CH_2Cl_2 at 0 °C → rt. Four reaction conditions were applied (Table 1), and iodine monochloride (ICl)[14] was found to give the best yield (79%, run 4) with 96% recovery. In all cases, significant amounts of by-products were not detected in ^1H NMR after precipitation of MPEG-bound molecules by the addition of diethyl ether. Because MPEG-OMTM **2** was completely consumed in these reactions, the remaining MTM group is supposed to be hydrolyzed. For a primary hydroxy group (Scheme 2), this reaction proceeded in better conversion yield (91%) with less equivalents of the substrate **5** using this optimized protocol. Substrates **3** and **5** used in excess amounts can be quantitatively recovered after the reactions. It should also be noted the introduction by ICl was so mild that the anomeric acetate functionality in **5** was not affected at all.



Scheme 2.

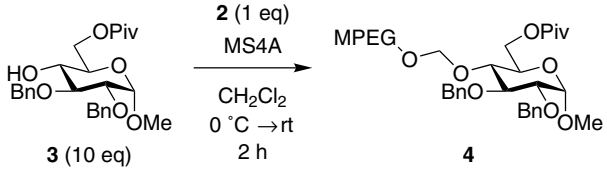


Scheme 3.

We then turned our attention to chemical reactions on the compounds attached to MPEG via CH_2 linker. At first, a pivaloyl group in **4** was removed under basic conditions (Scheme 3). This was realized by the use of tetrabutylammonium hydroxide at 40 °C to give **7** in a quantitative conversion yield with 98% recovery after precipitative work-up. Next, glucosylation to the monosaccharide **7** was attempted. As the glucosyl donor, two trichloroacetimidates (**8**, **9**) that have different protecting groups were used in the presence of 0.3 equiv of TMSOTf and MS4A in CH_2Cl_2. In the case of the donor **8**, the reaction proceeded smoothly at −40 °C to give the disaccharide **10** (α:β = 43:57) in a quantitative conversion with 96% recovery after precipitation. Glucosylation with a less reactive donor **9** also proceeded well at relatively higher temperature. Thus, the disaccharide **11** was obtained in 93% conversion with 100% recovery with exclusive β-selectivity. The by-product corresponding to the remaining 7% of **7** in the latter case was an *ortho* ester which is frequently observed in glucosylation with a 2-*O*-acyl donor. From these experiments the CH_2 linker is apparently useful for soluble polymer-based oligosaccharide synthesis because it is stable enough to the typical Lewis acid, TMSOTf.[15]

Efficient conditions for cleavage of the CH_2 linker to release the synthesized disaccharides were next investigated. The formylacetal is known to be one of the most stable acetals to acid hydrolysis. In addition, selective reaction conditions that do not affect the acid-sensitive carbohydrate anomeric functionality are necessary in

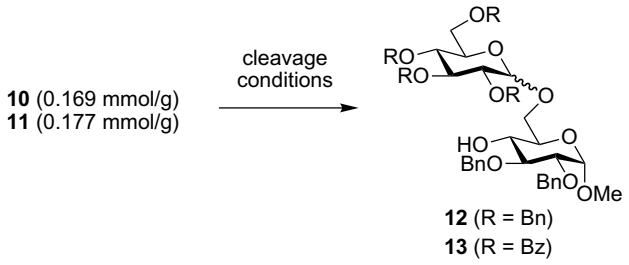
Table 1. Activation of MTM ether with various reagents to form formylacetal linkage between MPEG support and glucose derivative **3**



Run	Reagents	Conversion yield (%)
1	MeOTf (5 equiv)	67
2	NIS (4.3 equiv), TfOH (1.2 equiv)	67
3	$Me_2S^+SMe{\cdot}BF_4^-$ (5.8 equiv)	66
4	ICl (4 equiv)	79

Yields were determined by ^1H NMR. Weight-based recovery was >92% in all cases.

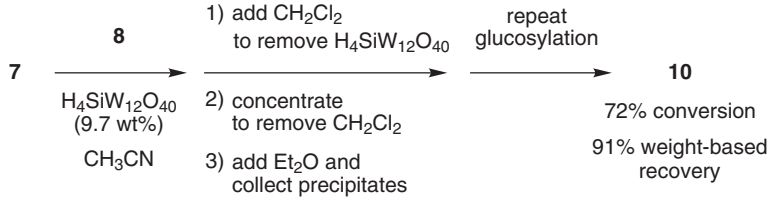
Table 2. Cleavage conditions to release disaccharides **12** and **13** from MPEG support



Run	Substrate	Reagents and conditions	Product and yield (%)
1	**10**	$MgBr_2$ or $ZnBr_2$ (30 equiv), CH_2Cl_2–Et_2O (1:2), rt	0% (no reaction)
2	**10**	$Sc(OTf)_3$ (0.8 equiv), CH_2Cl_2–Ac_2O (1:1), 0 °C → rt	0% (decomposed)
3	**10**	$FeCl_3$ (32 equiv), Ac_2O–$(CH_2Cl)_2$ (2:3), −20 → 0 °C	**14** (54%)
4	**10**	TMSI (4 equiv), CH_2Cl_2, −10 → 0 °C	**12** (65%)
5	**10**	$Ce(OTf)_x$ (40 wt.%), CH_3CN, rt	**12** (64%)
6	**10**	TFA–CH_2Cl_2 (3:7), 0 °C → rt	**12** (67%)
7	**11**	TFA–CH_2Cl_2 (3:7), 0 °C → rt	**13** (88%)

the present cases. The results for cleavage with various acids are summarized in Table 2. At first, $MgBr_2$[16] or $ZnBr_2$,[17] which are used for cleavage of the (2-methoxy)ethoxymethyl (MEM) protecting group,[18] were applied for the disaccharide **10** of 0.169 mmol/g (run 1). But they did not work at all, giving only recovered **10**. By the combination of $Sc(OTf)_3$ and Ac_2O that are used for the DOX linker,[6] cleavage of the CH_2 linker was realized, but the glucosidic linkage between two saccharide residues was also cleaved quantitatively (run 2). When rather strong $FeCl_3$[19] was used in place of $Sc(OTf)_3$, the desired disaccharide **12** was obtained in 54% isolated yield after silica-gel flash chromatography (run 3). The yield was improved by use of other simple Lewis acids, TMSI[20] (run 4) or $Ce(OTf)_x$[21] (run 5), providing the disaccharide **12** in 65% and 64% yield, respectively. As for **10**, the best yield was obtained by using a Brønsted acid, trifluoroacetic acid, which cleaved the CH_2 linker in 67% yield with accompanying small amounts (<20%) of monosaccharide by-products. These moderate cleavage yields are apparently due to the instability of the glucosidic linkage between the saccharide residues. When more stable **11** (0.177 mmol/g) bearing benzoyl protecting groups was exposed to trifluoroacetic acid in CH_2Cl_2, the undesired cleavage of the glucosidic bond was not detected at all, and the desired disaccharide **13** was isolated in good yield (88%) after chromatographic purification.[22] No epimerization was detected at the anomeric center of carbohydrates either. From these experiments, the use of a cocktail of trifluoroacetic acid–CH_2Cl_2 is the most efficient reagent for cleavage of the CH_2 linker so far to release synthesized molecules immobilized on the MPEG platform. Although the yield for acid-labile molecules such as **10** should be improved because it is not quite high enough (around 65%), it is noteworthy the reagent for this reaction and formaldehyde possibly generated are volatile. Once the cleavage has been done, simple precipitation followed by filtration using diethyl ether allows us to isolate the synthesized molecule.

Next we attempted to use this method to achieve glucosylation more efficiently. We anticipated that, in combination with reagents supported on another type of polymer, MPEG-supported organic synthesis would be operationally simpler. This was demonstrated by the glucosylation of the MPEG-bound **7** with the trichloroacetimidate donor **8** by using a solid acid, $H_4SiW_{12}O_{40}$ (Scheme 4).[23] The mixture was stirred at 0 °C → rt in CH_3CN until the donor **8** has been consumed (1 h). CH_2Cl_2 was then added to induce precipitation of the catalyst. After the solid acid was filtered off, the filtrate was once concentrated in vacuo. To the residue thus obtained was in turn added diethyl ether to precipitate the MPEG-bound molecule **10**. By this procedure, 91% yield of the MPEG support was successfully recovered and the reaction was found to proceed in 72% yield as judged from ^1H NMR after two cycles of glucosylation.



Scheme 4.

Although the yield requires improvement, this protocol is advantageous over the glucosylation using soluble acids such as those shown in Scheme 3 because the product can be isolated by a simple filtration procedure without liquid–liquid partition, and the *solid acid and the glucosyl donor-derived compound can be recovered independently*. We are further working along this type of an operationally simple procedures.

In conclusion, we have developed a new formylacetal (CH_2) linker for introducing small molecules to MPEG support. The preparation of the reagents, MPEG-OMTM **2**, was established in an easy and inexpensive way. This small linker allows attaching small molecules even via a hindered hydroxy group in good yield. The CH_2 linker is stable under typical acidic conditions employed for glycosylation, and can be specifically cleaved by a variety of reagents including volatile trifluoroacetic acid.[24] The use of this polymer support for realization of a library of small molecules directed toward chemical genetics is currently under way in our laboratory.

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