Silylene acetal from cheap reagents: synthesis and regioselective opening†

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In this communication, a practical method for using cheap and easily available silylene chlorides for diol protection is presented. The method is based on activation of the reagents using Finkelstein-like conditions. Silylene acetals of carbohydrates are synthesized, and it is furthermore shown how these can be regioselectively opened using Grignard reagents.

Introduction

Protective group chemistry plays a central role in organic chemistry and is a key tool in both peptide and carbohydrate chemistry. In particular, carbohydrate chemistry is dependent on selective protective group manipulations to ensure regio- and chemoselective reactions. The use of cyclic protective groups is particularly useful in polyols like carbohydrates as one can take advantage of the inherent stereochemistry and hence protect 2–3 alcohols at the same time in a selective manner. Cyclic acetals and ketals have therefore gained much popularity as they are introduced under mild acid catalysis and often with excellent selectivity, e.g. ketals predominantly protect vicinal cis diols, whereas acetals are selective for 1,3-diols, resulting in 5- and 6-membered rings, respectively. The cyclic acetals and ketals can also be removed under acidic conditions and are usually regarded stable under basic conditions. Another advantage of the commonly used cyclic ketals and acetals is the availability of well-developed methods for regioselective reductive and oxidative opening, liberating one alcohol. These reactions are key to differentiating the alcohols in carbohydrates and hence commonly used. Although methods for installing these protective groups under basic conditions have been developed, they are only used in special cases and often result in much lower yields than when using the common acid catalysed methods. An alternative to diol protection under basic conditions is to use silicon-based reagents. In carbohydrate chemistry, silyl ethers have become very important and often orthogonal groups to the commonly used alkyl ethers. One huge advantage is their introduction under mild basic conditions or even by metal catalysis from the silanes, in contrast to the often more harsh conditions used for alkylations. The applications of cyclic silyl-based protective groups have been exploited for decades, but have never reached the wide applications seen with ketals and acetals. Tetraisopropyldisiloxanylidene (TIPDS) ethers were introduced in the late seventies by Markiewicz for the protection of the carbohydrate part in nucleosides. Since then, TIPDS has found wider applications in general carbohydrate chemistry, where its influence in glycosylation reactions has been highlighted. One downside of using TIPDS is the formation of relatively big rings (7- or 8-membered) and the lability arising from the presence of an oxygen atom between the silicon atoms. A more stable alternative is the di-tert-butyl-silylene (DTBS), which has been successfully used for glycosyl donors, e.g. in β-arabinofuranosylations, α-galactofuranosylations, β-mannopyranosylations, and α-galactopyranosylations. In order to get the sterically demanding silylene installed, one has to use the more reactive (and expensive) di-tert-butylsilyl triflate as the reagent, which limits the scalability and generates fluorinated organic waste. Even when introducing the less hindered di-iso-propylsilylene, the chloride-based reagent is insufficiently reactive. As silyl chlorides find uses in technical applications, e.g. for silicon polymers, they are much cheaper than the corresponding triflates and also often cheaper than the corresponding silanes. Hence, more effective methods using the cheaper and more available silyl chlorides are attractive (Fig. 1).

In this paper, we study the activation of silylene chlorides using a Finkelstein-type approach, i.e. the addition of soluble iodide salts, which can exchange the chloride with the better leaving group iodide, driven by the precipitation of NaCl, and thereby promote the protection of diols. With access to silylene acetals, we perform a preliminary study on regioselective opening using Grignard reagents, which complements the methods used for ketals and acetals.

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Results and discussion

As di-tert-butyl silylene (DTBS) is among the most commonly used silylene acetal protective groups, its introduction in carbohydrates became our first goal (R = tert-Bu in Scheme 1). Based on the hypothesis that the reaction could be promoted by iodide salts in a Finkelstein-type reaction, we decided to use di-tert-butyl dichlorosilane as the reagent together with NaI and 2,6-lutidine as the base. As Trost and Caldwell have reported cleaner silylation in MeCN than in DMF, it became our first choice of solvent. MeCN has furthermore the advantage that it hardly dissolves NaCl, whereas NaI is dissolvable. This is key to facilitating a Finkelstein-type reaction (see the ESI† for the solubility of the relevant salt in different solvents). Phenyl 2,3-di-O-benzyl-β-D-thioglucopyranoside 1 was chosen as the substrate, as it represents a common functionalized carbohydrate. The reactions were performed at 80 °C and the progress was monitored by TLC. Reactions containing NaI were visibly faster reactions as determined from TLC, although full conversion of the diol 1 still took 11 days compared to 20 days without NaI. When changing the solvent to DMF, a faster reaction was observed in the absence of NaI and full conversion could be obtained after 5 days at 80 °C. To test product stability under these conditions, one reaction was left for 5 weeks at 80 °C with no decomposition of the product, which could be isolated as a colourless syrup in 72% yield. From these initial reactions it was clear that NaI had a positive effect on the rate of reaction in MeCN, but the slow protection reactions using the very bulky DTBS were not practical. In most cases, one would rather generate the silyl triflates in situ using AgOTf instead of waiting for days for full conversion. Hence, we turned our attention to much cheaper reagents, such as diphenyl-dichlorosilane and di-iso-propyl-dichlorosilane (DIPS), which only cost 1% and 5% of that of di-tert-butyl-silylene di-triflate, respectively. In addition, diphenyl-silylene di-triflate does not seem to be commercially available.

Under the standard conditions (Scheme 1), i.e. 2,6-lutidine as the base in MeCN at 50 °C, the DIPS protected thioglycoside 3 was obtained in a satisfactory isolated yield of 88% after overnight reaction (Scheme 1). Performing the same reaction using DMF as the solvent together with NaI gave a 31% isolated yield of 3. Leaving out NaI increased the yield to 48%, which suggests that the low solubility of NaCl in MeCN is responsible for the high yields and that we have a Finkelstein-type reaction.

To test the regioselectivity of the reaction, tetracel methyl α-D-glucopyranoside 4 was chosen as the next substrate (Scheme 2). In order to promote diol-protection, a close to stoichiometric amount of DIPSCI₂ was used together with 2,6-lutidine as the base. Performing the reaction at 50 °C without the addition of NaI resulted in 29% yield of 5 after 24 hours together with 9% yield of the undesired product 6. Addition of 3 equiv. of NaI under milder conditions at room temperature improved the yield of 5 to 41% and reduced the amount of the side product 6 to 5%. However, the reaction was slow, but this could be overcome by increasing the temperature to 50 °C and the amount of NaI to 5 equiv., which gave a 58% isolated yield of 5 together with only 5% yield of 6. To study diphenyl-dichlorosilane as the reagent, it was mixed with the tetraol 4 in DMF with tert-BuOK or NaH as the base (not shown). However, both conditions resulted in low conversion of the tetraol 4. The addition of HOBt (0.5 equiv.) did not increase the yield or rate of reaction, whereas AgOTf (1 equiv.) resulted in a faster reaction, but a complex reaction mixture. In addition, it was found that the diphenyl silylenes, when formed, were much less stable and hence were deprotected during flash chromatography on silica and basic aluminium oxide (see the ESI† for the NMR study on this). It was therefore decided to continue with the conditions shown in Scheme 2 using DIPS as the preferred protective group. MeCN was the preferred solvent as the precipitation of NaCl was clearly important for the outcome of the reaction.

With the conditions for protecting 4,6-diols in the gluco-series established, attention was shifted to galactosides, which upon 4,6-O-silylation would result in a less favourable cis-decaline bicyclic system. Hence, the diol 7 was protected using the standard conditions, resulting in a satisfactory 73% yield of the desired product 8 together with 10% yield of the TIPDS protected compound 9. When the α-mannoside 10 was treated under the standard conditions, the DIPS protected product 11 could be isolated in 81% yield after reaction overnight. To study whether regioselective protection of a triol was feasible,
the same conditions were used on the glucofuranoside triol 12, but surprisingly only the 3,5-O-silylene 13 could be isolated in a modest yield of 28%. The absence of the kinetic product, i.e. 5,6-O-silylene 14, suggests that the reaction is under thermodynamic control under the conditions used (Scheme 3). As the five membered tethering product was not observed, we assumed that it is significantly less stable. Attempts at synthesizing a 2,3-O-protected glucoside were therefore carried out (not shown), but no product could be isolated, which supports that the five-membered DIPS protection is indeed less favourable. This could be due to the strain produced when tethering *trans* vicinal diols, and we therefore proceeded to study *cis* vicinal diols. Attempts to protect the 2,3 positions in rhamnosides and the 3,4 positions in fucosides both failed, and even though some conversion could be observed, no products could be isolated. Hence, it seems like the reactions forming 5-membered rings are unfavourable and the products are unstable.

Mechanistic studies

The use of NaI clearly increased the rate and yields of the silylenations and the hypothesis was that more reactive iodosilanes were formed *in situ* in a Finkelstein-type reaction. To study this in more detail, $^{29}$Si-NMR spectra were recorded and the formation of iodosilanes could indeed be confirmed (see the ESI for details). The chemical shift change of 2,6-lutidine was also observed in the presence of DIPSCl$_2$ and there was a further change in the presence of both DIPSCl$_2$ and NaI (Fig. 2). The process of reaching equilibrium was slow; however, the exchange of 2,6-lutidine with silylene was fast on the NMR time scale as only one set of signals was observed despite the presence of sub-stoichiometric amounts of DIPSCl$_2$. An even further shift of 2,6-lutidine was observed under the standard conditions, suggesting that 2,6-lutidine is protonated during the silylation reaction. A positive effect of sodium could not be supported as the use of NaH as the base gave a low conversion. Next, the protection of the triol 10 was monitored by NMR under the standard conditions using CD$_3$CN as the solvent, and it was revealed that the 6-O-position is indeed silylated very fast, whereafter there is a slow migration to the 3,5-tethered product, which is in line with the isolated product 11 (see the ESI). Based on these observations, both iodide and 2,6-lutidine are important for the reaction rate and yield. MeCN is the preferred solvent due to its ability to dissolve NaI and the low solubility of NaCl, which is a prerequisite for a Finkelstein-type reaction.

Regioselective opening of silylenes

Acetals, and in particular benzylidenes, have gained much popularity as they are easy to install under acid catalysis and can be regioselectively opened under reductive or oxidative conditions. As outlined above, silylenes are complementary as they can be installed under mild basic conditions, but their regioselective opening has only been sporadically investigated and only a few examples involve complex multifunctional molecules like carbohydrates. Furasawa found that 3,5-O-DTBS protected nucleosides, when treated with TBAF, open stepwise with a silanol intermediate. Ziegler *et al.* showed that 4,6-O-TIPDS protected pyranosides followed a similar reaction path, although through a silyl fluoride intermediate. These studies were later followed up by other groups showing that the DTBS acetals open selectively, leaving the less hindered alcohol unprotected, when treated with fluoride sources. The selectivity is, however, limited to the opening of protected 1,3-diols.

A tempting alternative to the use of fluorides for opening silylene groups is the use of C-nucleophiles, which upon reaction give silyl ethers and a free alcohol. Mukaiyama *et al.* used alkyl lithium reagents, resulting in trialkyl silyl ethers. Later both Tanino *et al.* and Chando *et al.* have used alkyl lithium reagents for regioselective opening of silylenes.

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**Scheme 3** DIPS protection of galactopyranosides and glucopyranosides.
With easy access to dialkyl silylene protected carbohydrates, we attempted their regioselective opening using C-nucleophiles. Initially, the DTBS protected glucopyranoside S8 (see the ESI†) was used as the substrate, but neither MeMgBr, “turbo-Grignard” reagents, nor BuLi resulted in the conversion of the starting material under any of the conditions applied. Clearly, two tert-buty1 groups make the silicon too stable and essentially inert to strong C-nucleophiles. Consequently, the opening of DIPS protected thioglycopyranosides was studied next.

Initially, the DIPS protected thiogluco side 3 was treated with 5 equiv. of EtMgBr in THF, but no product formation could be detected after 2 days. Changing the solvent to toluene increased the reactivity of the Grignard reagent, and an ~1 : 0.15 mixture of the silyl ethers 15 and 16 could be isolated, with the 4-O-silyl ether 15 being the major product (Table 1). Using the smaller and more reactive MeMgBr resulted in lower selectivity (1 : 0.3) and a 36% isolated yield of 17 and 18. Turning to the thiogalactoside 8, the reaction with MeMgBr was much faster and leaving it at elevated temperature caused full desilylation to give the 4,6-diol 7. Hence, the reaction was carried out at room temperature, giving a mixture of two silyl ethers (19 and 20) and the diol 7 (9%) (Table 1). Interestingly, the 6-O-silyl ether 20 was now the major product. The difference in regioselectivity between gluco- and galacto-species can be explained by the different modes of complexation with magnesium under the reaction conditions in toluene. With gluco-stereochemistry, complexation with Mg2+ is limited to benzylic alcohols, illustrated by complexation with O3 and O4 in Fig. 3. However, with galacto stereochemistry, the 4-O- and 6-O-positions of compound 8, as well as the ring oxygen (O5), can chelate the magnesium ion (Fig. 3). The chelation with O5 makes it electron deficient, which influences the leaving group ability of O4, as partial negative charge here becomes more favourable. Furthermore, the 1,3-diaxial interaction in the galactopyranoside makes the 4-O-silylated product 19 sterically less favourable compared to the case of the glucopyranoside.

### Table 1  Regioselective opening of silylenes

<table>
<thead>
<tr>
<th>Substrate</th>
<th>R</th>
<th>T°C</th>
<th>Time</th>
<th>Ratioa</th>
<th>Yieldb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gluco: 3</td>
<td>Et</td>
<td>80</td>
<td>20 hours</td>
<td>~1 : 0.15</td>
<td>21%/3%</td>
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<tr>
<td>Galacto: 8</td>
<td>Me</td>
<td>rt</td>
<td>3 days</td>
<td>1 : 0.3</td>
<td>27%/9%</td>
</tr>
<tr>
<td>Manno: 11</td>
<td>Et</td>
<td>rt</td>
<td>4 hours</td>
<td>0.6 : 1</td>
<td>13%/29%</td>
</tr>
<tr>
<td>Gluco: 15 (Et), 17 (Me)</td>
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<tr>
<td>Galacto: 19 (Et), 20 (Et)</td>
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<td>Manno: 21 (Me), 23 (Et)</td>
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<td>Gluco: 16 (Et), 18 (Me)</td>
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<td>Galacto: 20 (Et), 23 (Et)</td>
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<td>Manno: 22 (Me), 24 (Et)</td>
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</table>

a The ratio (4-O-silyl ether/6-O-silyl ether) was determined from 1H-NMR of the crude product.
b Isolated yield (4-O-silyl ether/6-O-silyl ether).

When the silylene protected mannoside 11 was treated with MeMgBr in toluene, selectivity for the 4-OH 22 was observed (1 : 0.3 based on crude NMR). Using EtMgBr instead resulted in lower selectivity (1 : 0.8 based on crude NMR), but with a similar yield (Table 1). The reactivity of the mannoside seems faster, as judged by the shorter reaction time and the full conversion of the silylene acetal 11. When the reaction was left for a longer time, diol formation was also observed, as with 8. The higher reactivity and selectivity comparable to the galactoside 8 suggest that the 2-O-benzyl in 11 might also be involved in chelation of the Grignard reagent. A chelation involving O2 and O5 would have similar consequences to those with the galactoside, and can hence explain why these two sugars are more reactive in the Grignard reaction than the glucoside 3.

### Conclusions

In conclusion, we have developed a simple “Finkelstein-type” activation of cheap and easily available silylene dichlorides using NaI in MeCN. Using this method, diols can be protected under mild conditions without the need for the more expensive silylene triflate derivatives. The method works well with protected carbohydrate derivatives and seems to be under thermodynamic control when using tri- or tetra-ols. The formed silylene acetals can, besides being diol-protective groups, be regioselectively opened to a silyl ether and an alcohol using Grignard reagents.

### Author contributions

MLZ and DMF performed the experimental work. CMP supervised and wrote a draft of the manuscript. All contributed to the ESI† and the final version of the paper.

### Data availability

The data supporting this article have been included as part of the ESI†.

### Conflicts of interest

There are no conflicts to declare.
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