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9-Anthraldehyde acetals as protecting groups

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Abstract—Anthraldehyde acetals can be introduced regioselectively to carbohydrates in high yields. Advantages over conventional acetal protecting groups are increased crystallinity and strong absorbance and fluorescence which facilitate purification and reaction monitoring. The anthraldehyde acetals can be deprotected selectively in the presence of benzylidene acetals and can be cleaved regioselectively to yield 6-*O*-(9-anthracenyl)methyl ethers.

Chemical manipulation of polyfunctional organic compounds usually requires extensive use of protecting groups. These protecting groups should preferably be readily available, easily introduced and removed, well characterized, stable to a wide range of reactions, work-up and purification conditions and leave no by-products.[1] In addition, protecting groups can give the molecules specific properties such as crystallinity or enhanced traceability.

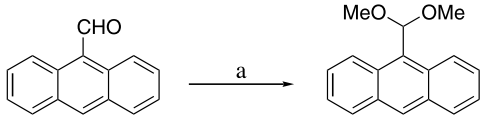
In order to facilitate reaction monitoring during the synthesis of carbohydrate derivatives on solid supports, we were looking for a protecting group which was required to be stable under basic conditions and be highly fluorescent, and thus, our attention was directed towards anthraldehyde acetals.

A number of aromatic acetals (e.g. benzylidene,[2] 4-methoxybenzylidene,[3] 2-nitrobenzylidene,[4] and benzophenone[5]) have been used as protecting groups in synthetic organic chemistry. These are easily introduced under slightly acidic conditions and can be cleaved using either acidic conditions to yield the diol or reductive or oxidative conditions to yield monoprotected compounds. However, the corresponding anthraldehyde acetals have so far not been used as protecting groups for diols.

Benzaldehyde dimethyl acetal has been shown to be a powerful reagent for introducing benzylidene acetals[6] and it was decided to use the analogous anthraldehyde dimethyl acetal **2**[7,8] for selective protection of diols. Anthraldehyde dimethyl acetal **2** was synthesized by treatment of anthraldehyde with trimethyl orthoformate under acidic conditions. The resulting anthraldehyde dimethyl acetal **2** was washed with methanol and isolated as pale yellow crystals in 82% yield (Scheme 1). The crystals grew darker[7] over time which did not seem to influence the yield of the protection step.

2-(Trimethylsilyl)ethyl β-D-glucopyranoside **3**[9] was protected with **2** by transacetalisation in MeCN catalyzed by *p*TSA to give **4** in 96% yield as a crystalline material (Scheme 2).

In order to study the stability of the new acetal protecting group, compound **4** together with the analogous benzylidene protected compound[9] as reference were subjected to acetic acid (80% in water). At 90°C, both the anthraldehyde acetal and the benzylidene acetal were completely deprotected in less than 5 min. However, at room temperature compound **4** was more than 95% deprotected in less than an hour, while the analogous benzylidene compound was deprotected to less than 5% in the same time, indicating that an anthraldehyde acetal can be selectively deprotected in the presence of benzylidene acetals. This is in full



1 **2**

Scheme 1. *Reagents and conditions*: (a) $(MeO)_3CH$, MeOH, Amberlite IR-120 H^+, 60°C, 15 h, 82%.

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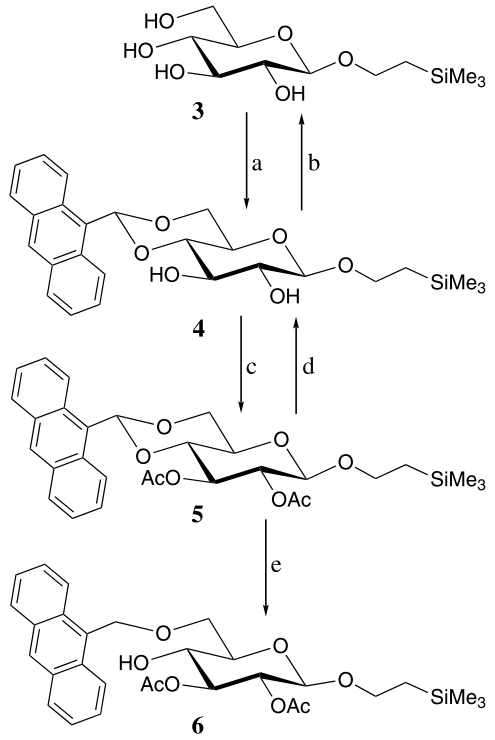
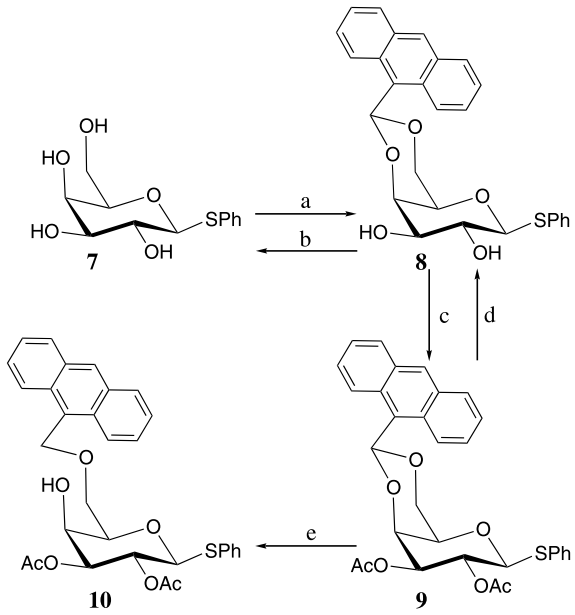


Scheme 2. *Reagents and conditions*: (a) **2**, MeCN, *p*TSA, 3 h, 96%. (b) AcOH (80%, aq.), 90°C, 2 h, 97%. (c) Pyridine, Ac_2O, 24 h, 98%. (d) NaOMe–MeOH (0.05 M), 2 h, 95%. (e) $NaBH_3CN$, THF, HCl/Et_2O, 2 h, 91%.



Scheme 3. *Reagents and conditions*: (a) **2**, MeCN, *p*TSA, 15 h, 94%. (b) AcOH (80%, aq.), 90°C, 1 h, 94%. (c) Pyridine, Ac_2O, 24 h, 97%. (d) NaOMe–MeOH (0.05 M), 1 h, 100%. (e) $NaBH_3CN$, THF, HCl/Et_2O, 2 h, 57%.

agreement with earlier observations where electron releasing groups gave faster acetal hydrolysis.[3] Deprotection of compound **4** using standard conditions (90°C) gave compound **3** in 97% yield.

Compound **4** was then acetylated using Ac_2O/pyridine to give **5** in 98% yield. In order to confirm the base stability of the anthraldehyde acetal, **5** was deacetylated (NaOMe–MeOH) to restore **4** in 95% yield.

In order to test if the anthraldehyde acetal could be selectively cleaved under reductive conditions, **5** was subjected to $NaBH_3CN/THF/HCl/Et_2O$[10] which gave the 6-*O*-(9-anthracenyl)methyl ether **6** in 91% yield.†

The same reaction sequence (a–e) was repeated using phenyl 1-thio-β-D-galactopyranoside **7**[11] which gave similar yields (Scheme 3). The galactose acetal **8** seemed to be slightly more stable towards acidic hydrolysis compared to the corresponding glucose derivative **4**. Deprotection using acetic acid (80% in water at room temperature) required 2 h to give more than 95% deprotection. The corresponding benzylidene acetal[12] showed less than 5% deprotection during the same reaction time, again indicating selective deprotection.

Reductive opening of the galactose acetal **9** gave compound **10** in a modest 57% yield, despite several attempts to optimize the yield. There is at present no explanation for this observation.‡

All synthesized compounds **3**–**10** were easily crystallized and were highly fluorescent. They could be followed

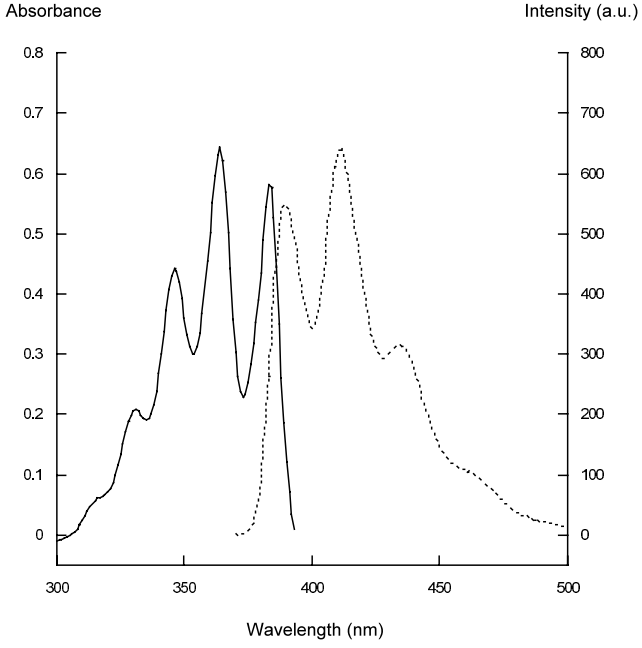


Figure 1. Absorbance spectrum of compound **5** (0.10 mM in MeCN, solid line) and fluorescence spectrum of compound **5** (0.010 mM in MeCN, $\lambda_{Ex} = 364$ nm, dotted line).

† The structure of compound **6** was confirmed using two-dimensional NMR techniques.

‡ The structure of compound **10** was confirmed using two-dimensional NMR techniques. Regioselective reductive opening of the corresponding benzylidene compound gave a moderate 70% yield.

during chromatography by simply using a hand-held UV-lamp to illuminate the column. The absorbance ($\varepsilon_{max} = 6440$ M^{-1} (364 nm)) and fluorescence spectra were recorded from a solution of compound **5** in MeCN (Fig. 1).[13,14]

Anthraldehyde dimethyl acetal 2. Anthraldehyde (3.09 g, 15 mmol) and trimethyl orthoformate (1.86 mL) were dissolved in MeOH (15 mL) and Amberlite IR-120 H^+ (75 mg) was added and the mixture was stirred at 60°C for 15 h. The mixture was cooled to rt and CH_2Cl_2 (10 mL) was added. The solution was filtered and concentrated. MeOH (25 mL) was added and the mixture was cooled to −20°C and the product was filtered and washed with MeOH (−20°C) to give **2** (3.09 g, 82%). ^{13}C NMR ($CDCl_3$): δ 131.91, 130.36, 129.62, 129.43, 126.40, 125.32, 125.29, 104.60, 56.32.

2-(Trimethylsilyl)ethyl 4,6-*O*-(9-anthracenyl)methylene-β-D-glucopyranoside 4. To a solution of **3** (325 mg, 1.16 mmol) and **2** (367 mg, 1.45 mmol) in MeCN (10 mL) was added *p*TSA (5 mg) and the mixture was stirred at rt for 3 h and then neutralized by addition of Et_3N and concentrated with toluene three times. The residue was chromatographed (SiO_2, toluene→6:1 toluene–acetone) to give **4** (519 mg, 96%). A sample was recrystallized from ether–heptane; mp 107–108°C. $[\alpha]_D^{20}$ −34 (*c* 1.3, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 8.63 (dd, 2H, *J* 9.1, 0.9 Hz, H-1′, H-8′), 8.48 (s, 1H, H-10′), 8.00 (dt, 2H, *J* 8.3, 0.7 Hz, H-4′, H-5′), 7.53, 7.45 (ddABq, 2H each, *J* 8.8, 6.5, 1.5 Hz, H-2′, H-3′, H-6′, H-7′), 6.94 (s, 1H, ArCH), 4.54, (dd, 1H, *J* 10.3, 4.5 Hz, H-5), 4.50 (d, 1H, *J* 7.8 Hz, H-1), 4.05 (ddd, 1H, *J* 11.2, 9.6, 6.0 Hz, $OCH_2CH_2SiMe_3$), 4.00 (t, 1H, *J* 10.0 Hz, H-4), 3.85–3.95 (m, 1H, H-3), 3.81, 3.76 (ABq, 1H each, *J* 9.1 Hz, 2*H-6), 3.70 (ddd, 1H, *J* 11.2, 9.6, 6.0, $OCH_2CH_2SiMe_3$), 3.55 (ddd, 1H, *J* 8.8, 7.8, 2.4 Hz, H-2), 2.75 (d, 1H, *J* 2.3 Hz, HO-3), 2.55 (d, 1H, *J* 2.4 Hz, HO-2), 1.10, 1.05 (ddABq, 1H each, *J* 13.6, 10.8, 6.0 Hz, $OCH_2CH_2SiMe_3$), 0.06 (s, 9H, $SiMe_3$). ^{13}C NMR ($CDCl_3$): δ 131.92, 130.50, 130.09, 129.52, 126.85, 126.70, 125.35, 125.15, 103.18, 101.07, 82.32, 74.97, 73.66, 70.25, 68.45, 67.04, 18.76, −0.95. HRMS calcd for $C_{26}H_{32}O_6Si$ (M+Na): 491.1866; found: 491.1861.

To summarize, anthraldehyde acetals can be introduced selectively to carbohydrates in high yields, induce crystallinity and show strong absorbance and fluorescence. The anthraldehyde acetals can be deprotected selectively in the presence of benzylidene acetals and can be cleaved regioselectively to yield 6-*O*-(9-anthracenyl)-methyl ethers.

Acknowledgements

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