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ArSCl-Mediated Coupling of *exo*-Glucal with *O*- and *C*-Nucleophiles

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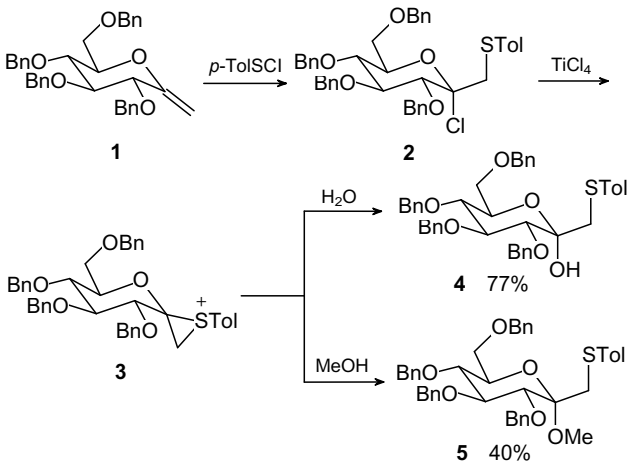
The reaction of ArSCl adducts of *exo*-glucal with *O*- and *C*-nucleophiles leads to a stereoselective preparation of ketopyranoside derivatives and 1,1-*gem*-disubstituted *C*-glucosides, respectively.

Bridged intermediates derived *via* the Ad_E route from 1,2-unsaturated carbohydrate derivatives (glycals) are widely employed as electrophilic agents for the preparation of various *O*- and *C*-glycosides.[1] Much less is known about Ad_E reactions of 1-*exo*-methylene carbohydrate derivatives (*exo*-glycals) and only in a few cases have the corresponding adducts been used for glycosylation. Thus, several *C*- and *O*-glycosides were prepared as a result of iodonium ion-promoted reactions of some *exo*-glycals.[2a,b] A new approach to ketofuranosyl glycosides and disaccharides was suggested based on the transformation of *exo*-glycals into the respective epoxide followed by the Lewis acid mediated reaction of the latter with alcohols.[2c] A glycosyl cation generated from 1-*exo*-methylene carbohydrate derivatives under the action of Lewis acid was shown to be capable of reacting with the second molecule of *exo*-glycal to give the respective *C*-disaccharide. Only symmetrical coupling was shown to be achievable by this route.[2d,e]

Recently we described a novel approach to a stereoselective synthesis of 2-deoxy-*C*-β-*gluco*-pyranosides based on the use of ArSCl adducts of *endo*-glucal derivatives as electrophiles for glucosylation of various *C*-nucleophiles.[1c] Application of this reaction to *exo*-glycals might offer novel opportunities for the stereoselective preparation of ketopyranoside derivatives (employing *O*-nucleophiles) and 1,1-*gem*-disubstituted *C*-glycosides (using *C*-nucleophiles). Here we report preliminary results attesting to the promise of this approach.

The starting compound, *exo*-glucal (**1**, 2,6-anhydro-3,4,5,7-tetra-*O*-benzyl-1-deoxy-D-*gluco*-hept-1-enitol), was synthesized in three steps in overall yield *ca.* 50% from methyl-α-D-*gluco*-pyranoside as described earlier.[3] To the best of our knowledge reaction of **1** with ArSCl has never been tried before. It was found that the interaction of **1** with *p*-TolSCl took place readily upon mixing the reagents in a CH_2Cl_2 solution at −40 °C to give the adduct **2**. The latter was used in further reactions without additional purification.‡

As with ArSCl adducts derived from other vinyl ethers,[5] the adduct **2** under the action of Lewis acid is converted into an active electrophilic species, an episulfonium ion-like intermediate **3**, which can be further intercepted by some external nucleophiles. Thus, treatment of **2** with $TiCl_4$ followed by quenching with water gave 2,3,4,6-tetra-*O*-benzyl-1-oxy-1-(*p*-tolylthio)methyl-α-D-*gluco*-heptulopyranoside **4** as a single isomer in 77% yield. A similar reaction performed with MeOH used as a quencher yielded the corresponding methoxy derivative **5** (Scheme 1).



Scheme 1

We have also found that the electrophile **3** is capable of reacting not only with *O*-nucleophiles but with a set of typical

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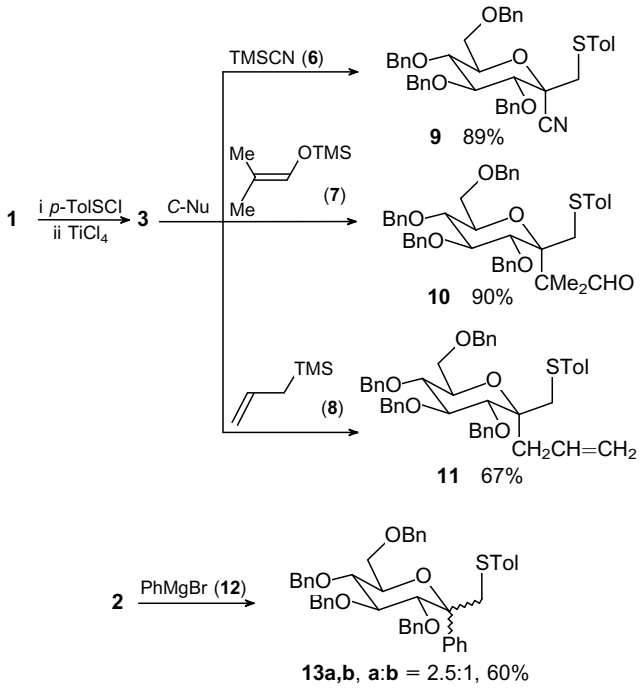
‡ Thus far we do not have any direct evidence on the structure of adduct **2** as well as ESI **3** derived therefrom. However, the stereochemistry of the final products (*vide infra*) is in full accord with the suggested structures of **2** and **3**.



Scheme 2

Si-containing carbon nucleophiles **6**–**8** to give the corresponding 1,1-disubstituted carbon glycosides **9**–**11** in good to excellent yields. In the case of a more active nucleophile such as Grignard reagents it is not necessary to generate intermediate **3**. Thus, the coupling of adduct **2** with phenylmagnesium bromide **12** proceeds in the absence of Lewis acid and leads to the formation of phenylated adduct **13** as a mixture of two isomers in good yield.

The structures of compounds **4**, **5** and **9**–**11** were established *via* consistent NMR (^{1}H and ^{13}C) spectroscopic data and HRMS determinations. In all cases the formation of a single stereoisomer was observed (within the limits of the accuracy of evaluation by NMR spectroscopy). The stereochemistry of geminal substituents at C-1 in the products prepared as shown above was ascertained by the observation of noticeable NOE at the proton signal at C-2 on irradiation of CH_2S group protons.[§]

The results described in this communication demonstrate the efficiency of the utilization of *exo*-glucal–ArSCl adducts as electrophiles for the stereoselective formation of derivatives containing a β-arylthiomethyl group and an α-bound nucleophilic moiety. One can easily envisage the obvious ramifications for the synthetic utilization of these products owing to the presence of various functional substituents such as cyano or carbonyl groups, double bonds or aryl residue as well as the arylthio group. It is also to be emphasized that the previously published data on the reactivity pattern of ESI intermediates derived from unsaturated compounds of various types[4] leaves little doubt that a much wider set of nucleophiles other than those used in the present study might be also applicable as quenchers for intermediate **3**. The new option elaborated for the highly stereoselective formation of a *C*-glycosidic bond seems to be of special importance in view of the current interest in the synthesis of various *C*-glycosides as chiral intermediates for the preparation of natural compounds and their analogues with a promising pattern of biological activity.[5]

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[§] A typical experimental procedure is as follows. To a solution of *p*-TolSCl (0.0397 g, 0.25 mmol) in CH_2Cl_2 (1 ml) at −78 °C was added a solution of **1** (0.134 g, 0.25 mmol) in CH_2Cl_2 (10 ml). After 10 min a solution of TMSCN **6** (0.049 g, 0.50 mmol) in CH_2Cl_2 (2 ml) was added followed by dropwise addition of $TiCl_4$ (0.04 ml, 0.30 mmol) in CH_2Cl_2 (2 ml). The mixture was stirred for 3 h at −40 °C, quenched with aqueous $NaHCO_3$ and extracted with diethyl ether. The usual work-up and preparative TLC on SiO_2 gave adduct 1-cyano-2,3,4,6-(tetra-*O*-benzyl)-1-(*p*-tolylthio)methyl-D-*gluco*-pyranoside (**7**, 0.119 g, yield 70%), R_f 0.53 (hexane–ethyl acetate, 4:1). IR (neat): 2347 cm^{-1} (CN); ^{1}H NMR (250 MHz): 2.34 (s, 3H, Me), 3.28 and 3.46 (2 × d, J_{AB} 13.5 Hz, 2H, SCH_2), 3.675 (dd, $J_{5,6b}$ 1.5 Hz, $J_{6a,6b}$ 12 Hz, 1H, H^{6b}), 3.80 (d, $J_{2,3}$ 9 Hz, 1H, H^2), 3.84 (dd, $J_{5,6a}$ 3 Hz, $J_{6a,6b}$ 12 Hz, 1H, H^{6a}), 3.825 (t, $J_{3,4}=J_{4,5}$ 9 Hz, 1H, H^4), 3.95 (ddd, $J_{4,5}$ 9 Hz, $J_{5,6a}$ 3 Hz, $J_{5,6b}$ 1.5 Hz, 1H, H^5), 4.06 (t, $J_{2,3} = J_{3,4}$ 9 Hz, 1H, H^3), 4.73 (2 × m, 8H, OCH_2Ph), 7.40 (m, 24H, H_{arom}); ^{13}C NMR (75 MHz): 20.76 (Me), 41.40 (CH_2S), 67.87, 73.17, 74.78, 75.04, 75.56 (1 group of OCH_2 and 4 groups of OCH_2Ph), 76.76, 77.08, 79.04, 84.325 (4 groups of OCH), 95.85 (C^1), 116.274 (CN), 127.33, 127.46, 128.16, 129.38, 131.15, 131.88, 132.52, 136.77, 137.07, 137.45, 137.52, 137.66, 137.79, 137.88, 137.93 (C_{arom}); HRMS: Calc. for $C_{43}H_{43}O_5S_1N_1$ (M^+) *m*/*z* 685.2851, found *m*/*z* 685.2846.

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