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ONE STEP C-ACYLATION OF GLYCALS AND 2-DEOXY-HEXOPYRANOSES AT C-2

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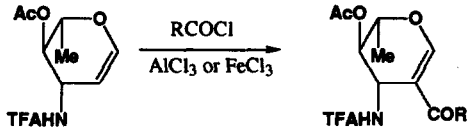
Abstract: A simple method has been developed for synthesizing previously unknown 2-*C*-acyl glycals. Direct Friedel-Crafts acylation of glycals with acetyl chloride or acetic anhydride in the presence of $AlCl_3$ or $FeCl_3$ gave 2-*C*-acetyl-hex-1-enitols in yields often better than 80%-90%. Interestingly, the 2-*C*-acetyl-hex-1-enitols can also be prepared in a single step from 1-*O*-acetyl- and 1-*O*-silyl-2-deoxy-hexopyranoses, and for all reactions excellent yields were observed.

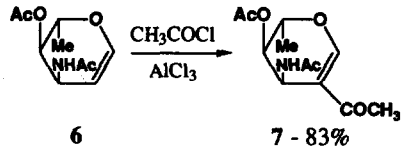
Even though the Friedel-Crafts reaction[2] was discovered well over 100 years ago and has been successfully used by generations of chemists to functionalize aromatics, its application to acylate alkenes, because of low yield and lack of selectivity, has been limited[2-4]. More encouraging news in recent years indicated the potential for the development of synthetically useful applications of Friedel-Crafts acylation of alkenes.[5-10]

Glycals were interesting targets for at least two reasons. First, the electrophilic addition reaction to a double bond of glycal is regioselective,[11] and second, because of the elimination of substituent from C-1, only one product is possible. The major problem of standard, commercially available glycals like 3,4,6-tri-*O*-acetyl-D-glucal or 3,4-di-*O*-acetyl-L-rhamnal is the tendency to undergo allylic rearrangement and related reactions in the presence of Lewis acids.[12] Therefore, in our initial studies[13] we focused on C-acylation of relatively stable glycals containing a substituted amino group at the C-3 position.



1

2 - R = CH_3; 96% ($AlCl_3$); 88% ($FeCl_3$)
3 - R = $(CH_2)_2CH_3$; 90% ($AlCl_3$)
4 - R = $(CH_2)_{12}CH_3$; 90% ($AlCl_3$)
5 - R = $(CH_2)_{16}CH_3$; 90% ($AlCl_3$)



6

7 - 83%

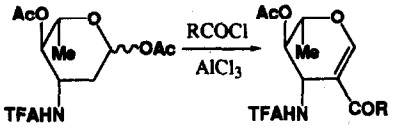
The 4-*O*-acetyl-1,5-anhydro-2,3,6-trideoxy-3-*N*-trifluoroacetamido-L-arabino-hex-1-enitol (**1**)[14] and 4-*O*-acetyl-1,5-anhydro-2,3,6-trideoxy-3-*N*-acetamido-L-ribo-hex-1-enitol (**6**)[14] were reacted with acetyl chloride in the presence of $AlCl_3$. Reactions led to the formation of 2-*C*-acetyl-glycals **2** and **7** with excellent

yields of 96% and 83%, respectively.[15] Glycal **1** was also reacted in the presence of $FeCl_3$. The yield of **2** was slightly lower (88%) than that for $AlCl_3$. Glycal **1** was further reacted with acyl chlorides of varying alkyl chain length. The yields of butyroyl, myristoyl and stearoyl 2-*C*-substituted products **3**, **4**, and **5** were similarly high (90-92%). All compounds were crystalline with sharp melting points.[15]

C-Acylation of glycals. Typical procedure.[16]

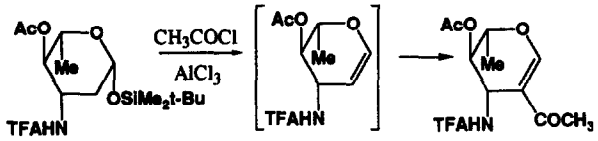
4-*O*-acetyl-1,5-anhydro-2,3,6-trideoxy-3-*N*-trifluoroacetamido-L-arabino-hex-1-enitol (**1**, 110 mg, 0.41 mmol) was placed in the reaction vessel together with $AlCl_3$ (100 mg, 0.75 mmol, Aldrich Cat. No. 29,471-3). Acetyl chloride was added (2 mL), and the mixture was stirred at r.t. for 30 sec. and left unattended for 10 minutes (all operations were performed in glove box under dry nitrogen). The reaction was stopped by addition of 50 mL of $CHCl_3$ and washing with aq. solution of sat. $NaHCO_3$. TLC showed presence of one product (Rf 0.18, toluene-ethyl acetate 4 : 1; Rf 0.60, toluene-acetone 2 : 1). The organic solution was dried with anhydrous sodium sulfate, filtered, and evaporated under diminished pressure to give a crystalline residue of 4-*O*-acetyl-*C*-2-acetyl-1,5-anhydro-2,3,6-trideoxy-3-*N*-trifluoroacetamido-L-arabino-hex-1-enitol (**2**)[15], which was purified by crystallization. Yield: 122 mg (96 %, mp 203-204 °C).

Realizing that the 1-*O*-acyl-2-deoxy-hexopyranoses and their respective glycosyl halides undergo elimination with relative ease under various conditions[14], we examined whether 1-*O*-acetyl-hexopyranose **8** could be used as a possible substrate for a Friedel-Crafts type of substitution. Reaction was initially examined for acetyl chloride in combination with $AlCl_3$. We observed substantial increases in the reaction time (over 1 hr) when compared with glycal **1** (less than 10 min.); however, the yields remained fairly high (90-95%). Reaction of **8** with myristoyl chloride also gave the proper product, **4**, with a yield of 86%.



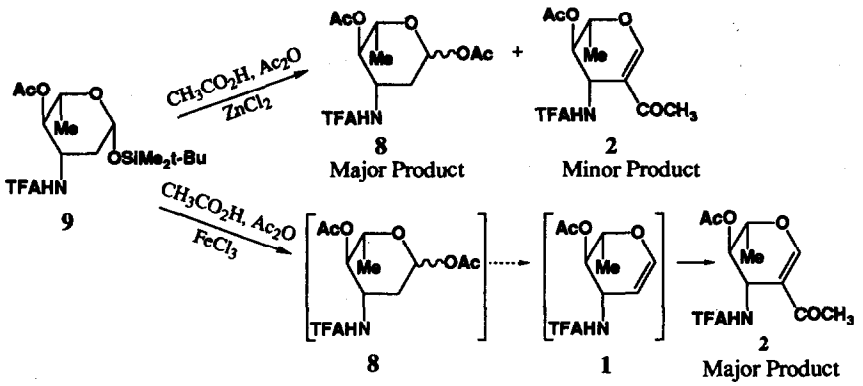
8

2 - R = CH_3; 95%
4 - R = $(CH_2)_{12}CH_3$; 86%

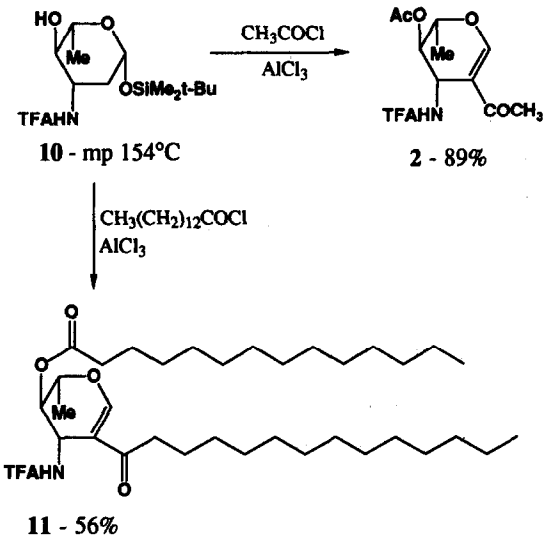


9 **1** **2** - 96%

Similarly successful was C-acylation of 1-*O*-*t*-butyldimethylsilyl-2-deoxy-hexopyranose **9**[17], and 2-*C*-acetylated product **2** was isolated with yield of 96%. It seems reasonable to assume that in both reactions starting from 2-deoxy-hexopyranoses **8** and **9**, the intermediate product is glycal **1**. Elimination appeared to be much slower than C-acylation; therefore, the intermediate glycal could not be detected in the reaction mixtures.



To slow down the process of C-acylation, milder acylation conditions were selected. Reaction of **9** with acetic anhydride/acetic acid in the presence of $ZnCl_2$ gave C-acetylated product **2** as a minor and 1-*O*-acetyl-hexopyranose **8** as a major product. No glycal **1** could be observed. This indicates that under such conditions formation of glycal **1** is the slowest process of all, and acetolysis of **9** to **8** is the fastest. Using $FeCl_3$ instead of $ZnCl_2$ as the catalyst, increased the rate of C-acylation, and in the reaction of **9**, the 2-C-acetyl-glycal **2** was isolated as a major product. Therefore the C-acylation of 1-*O*-silylated 2-deoxy-hexopyranoses could be an efficient four-step reaction involving acetolysis, elimination of CH_3CO_2H, addition of acyl chloride, and elimination of HCl, in that order.



To further challenge this approach, the level of complication was increased by using a substrate containing a free hydroxyl group at C-4. 1-*O*-Silylated-2-deoxy-hexopyranose **10** in the reaction with acetyl chloride/$AlCl_3$ gave, as expected, 4-*O*-acetylated product **2** (98%). The usefulness of such a reaction is further

demonstrated in the reaction of **10** with myristoyl chloride to give dimirystoyl derivative **11** (yield, 56 %).

To conclude, the Friedel-Crafts acylation of alkenes appears to be a very useful reaction for preparing a variety of potentially useful 2-C-substituted sugar derivatives from glycals as well as directly from 2-deoxy-hexopyranoses.

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References and Notes

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14. Glycals **1** and **6** were prepared using method described by D. Horton, W. Priebe, and M. Sznaidman, *Carbohyd. Res.*, **1989**, *187*, 145.
15. NMR spectra were recorded for solution in chloroform-d (internal standard Me_4Si) with QE 300 or Nicolet NT 300 spectrometer operating at 300 and 75 MHz for ^1H and ^{13}C nuclei, respectively, unless otherwise stated. All compounds gave correct elemental analysis. Analytical data for selected compounds: Data for **2**: mp 204 °C; $[\alpha]^{25}_D$ - 114.2° (c=1.2, CH_2Cl_2); ^1H NMR: δ 7.69 (s, 1 H, H-1), 6.20 (d, 1H, NH), 5.22 (t, 1H, $J_{3,4}=J_{4,5}$ 5.9 Hz, H-4), 4.82 (t, 1H, ΣJ=12.7 Hz, H-3), 4.35 (dq, 1 H, H-5), 2.27 (s, 3H, C-Ac), 2.11 (s, 3 H, O-Ac),1.39 (d, 1 H, $J_{5,6}$ 6.9 Hz, H-6). Data for **3**: mp 144 °C; $[\alpha]^{25}_D$ - 110.3° (c=1.3, $CHCl_3$). Data for **4**: mp 141 °C; $[\alpha]^{25}_D$ - 71.7° (c=1.1, $CHCl_3$). Data for **5**: mp 140 °C. Data for **7**: mp 88 - 90 °C. Data for **11**: mp 105 °C; $[\alpha]^{25}_D$ - 55.9° (c=0.6, $CHCl_3$).
16. Reaction conditions for 2-deoxy-hexopyranoses were similar; however, the reaction times were substantially longer (hours instead of minutes).
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