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SYNTHESIS OF ISOCHROMANE DERIVATIVES BY METALLOCENE-PROMOTED REACTION OF 2-ALKOXY-2-FLUORO-GLYCOSYL FLUORIDES WITH BENZYL ALCOHOL

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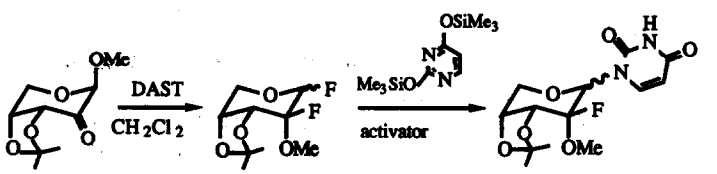
Abstract: *Isochromane derivatives have been obtained by reaction of glycosyl fluorides with benzyl alcohol in presence of Cp_2HfCl_2/ $AgClO_4$, by a glycosylation, migration, and intramolecular cyclization sequence.*

Glycosyl fluorides have become current starting materials for glycosylation reactions, since in the last ten years methods for the activation of the anomeric fluorine atom were developed.[1] Recently, we have shown that different α-pyranosyl-2-uloses react with diethylaminesulfur trifluoride (DAST) to give 1,2-difluoro carbohydrates.[2] Thus, ulose **1** can be converted into glycosyl fluoride **2** in 72% yield (Scheme 1). Compound **2** shows two fluorine atoms geminal to alkoxy groups, so that chemoselectivity problem may arise in fluorine substitution reactions; however, secondary fluorine could be selectively activated with metallocene derivatives (Cp_2MCl_2/AgX; M=Hf, Zr; X=ClO_4, TfO) to give pyranosyl nucleosides by reaction with bis(trimethylsilyl)uracil[3] (Scheme 1).



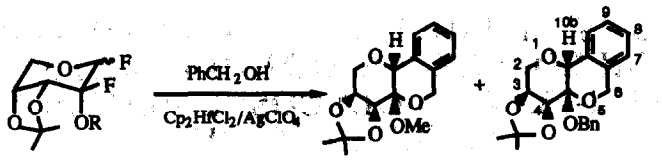
1 **2** **3**

Scheme 1

In the carbohydrate field the interest in C-2 fluoro analogues is justified by the unusual stability to acidic hydrolysis of α-fluoro ketals and acetals,[4] which makes more difficult the degradation of carbohydrate containing antibiotics. We envisaged that metallocene activators could be used for the selective glycosidation compound **2** to obtain a novel class of glycosides with a 2-fluoro-2-methoxy substitution on the C-2 of the sugar ring.

Initial attempts to glycosylation of **2** with cyclohexanol using $Cp_2HfCl_2/AgClO_4$ gave a complex mixture. However, when benzyl alcohol was utilized, a mixture of **4** and **5**[5] was obtained in 81 % yield (Scheme 2). Use of either a lower $PhCH_2OH$/sugar ratio or a different $Cp_2HfCl_2/AgClO_4$ ratio gave the same cyclization products

in lower yields but only small changes in the **4/5** ratio were observed (Table 1). Compound **4** was favoured when benzene at 10 °C rather than CH_2Cl_2 at -50 °C was employed.



2 4 5

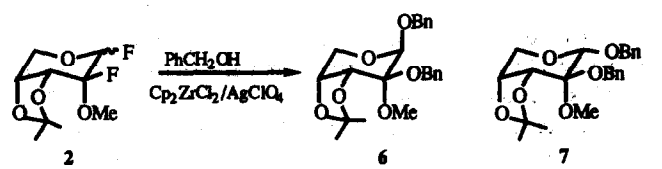
Scheme 2

Table 1. Reaction of **2** with Benzyl Alcohol and $Cp_2HfCl_2/AgClO_4$.

2	Molar ratio Cp_2HfCl_2	$AgClO_4$	$PhCH_2OH$	Solvent	Temp.	Yield[a] (%)	4/5[b]
1	1	2	2	CH_2Cl_2	-50°C→rt	82	7/10
1	1	2	1	CH_2Cl_2	-50°C→rt	54	10/7.5
1	1	1	1	CH_2Cl_2	-50°C→rt	39	7/10
1	1	2	2	benzene	10°C→rt	39	10/4

[a] Isolated yield after preparative TLC or Flash cromatography.
[b] Ratios were determined by ^1H NMR (integration of protons 10b).

Surprisingly, with $Cp_2ZrCl_2/AgClO_4$ dibenzyl derivatives **6** and **7** were the major products (Scheme 3).



2 6 7

Scheme 3

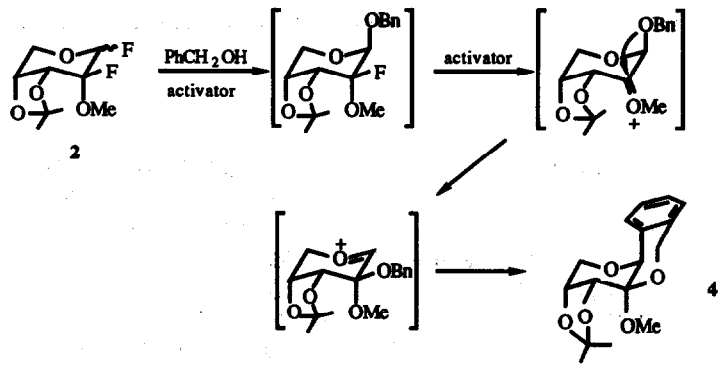
Table 2. Reaction of **2** with Benzyl Alcohol and $Cp_2ZrCl_2/AgClO_4$.

2	Molar ratio Cp_2ZrCl_2	$AgClO_4$	$PhCH_2OH$	Solvent	Temp.	Yield[a] (%)	6/7[b]
1	1	2	2	CH_2Cl_2	-50°C→rt	89	10/6
1	1	2	1	CH_2Cl_2	-50°C→rt	42	10/9

[a] Isolated yield after preparative TLC or Flash cromatography.
[b] Ratios were determined by ^1H NMR (integration of the anomeric proton).

Taking into account preliminary results shown in Scheme 1[3], it is reasonable to assume that the attack of benzyl alcohol at the anomeric position takes place first. Thus, **4** may arise from the following sequence of

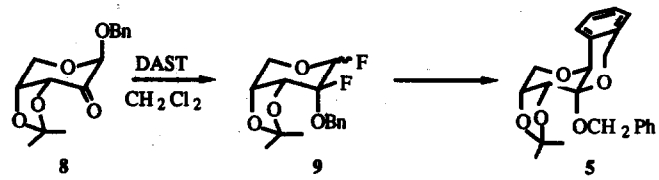
events: activation of F-2, 1,2-migration of the anomeric substituent, and intramolecular Friedel-Crafts type cyclization (Scheme 4). Obtention of **5** should involve an additional transacetalization reaction. On the other hand, no reaction has been observed when compounds **6** and **7** were treated with $Cp_2HfCl_2/AgClO_4$.



Scheme 4

The structures of **4** and **5** are supported by: (a) the lack of fluorine in both products; (b) the absence of the C-1 signal at ~100 ppm, together with the presence of 4 CH and 2 quaternary carbons for the aromatic carbons in the ^{13}C NMR spectra of **4**; (c) the value of geminal coupling constant of the benzyl methylene group[6] is ~15 Hz for **4**, whereas they are of 15 Hz and 12 Hz for the AB systems in **5** (for **7** and **8** J_{AB} values are12 Hz); and (d) a nOe is detected in **5** between H-1, a methyl of the isopropylidene group and one proton of the acyclic methylene system.

The intramolecular Friedel-Crafts cyclization of 2-O-benzyl-protected carbohydrates is a well documented process that has recently attracted attention.[7] However, the pyranoid systems have shown to be less reactive than furanoid ones, requiring activated benzyl groups to carry out that cyclization.[8] Also, intramolecular cyclization processes have been described from tri-O-benzyl-α-D-*ribo*-furanosyl fluoride[9] in presence of $BF_3.Et_2O$ and from tetra-O-benzyl-α-D-*manno*-pyranosyl fluoride[10] using $Cp_2ZrCl_2/AgClO_4$.



Scheme 5

In order to gain insight into this process, O-benzyl derivative **8** was converted to **9** in a similar way[2] to compound **2** in 68% yield. Compound **9** could give rise directly to tricyclic compounds by Friedel-Crafts reaction. Treatment of **9** with $Cp_2HfCl_2/AgClO_4$ in the absence of benzyl alcohol, following the usual methodology, gave **5** as the only identifiable product in 17 % yield. This indicated that a debenzylation process had taken place. Use of other fluorine activators such as $BF_3.Et_2O$, Tf_2O and TMSOTf, afforded small amounts of cyclization product together with large amounts of degradation products. When one mol of benzyl alcohol was added to the reaction mixture, **5** was obtained in 71 % yield.

Further work exploring the behavior of 1,2-difluoro carbohydrates for the synthesis of cyclic compounds is in progress.

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5 All new compounds were fully characterized by ^1H and ^{13}C NMR, IR and Elemental Analysis. Selected data for **4** and **5** follow:
4: ($CDCl_3$, 200 MHz), δ 7.45-7.20 (m, 4H, H_{Ar}), 4.88 (ddd, 1H, J_{3-4}= 6.0 Hz, J_{3-2ax}= 3.5 Hz, J_{3-2eq}= 0.5 Hz, H_3), 4.87 (d, 1H, $J_{6,6'}$= 15.3 Hz, H_6), 4.76 (d, 1H, $H_{6'}$), 4.68 (d, 1H, H_4), 4.19 (s, 1H, H_{10b}), 3.94 (dd, 1H, $J_{2eq-2ax}$= 10.3 Hz, J_{2eq-3}= 0.5 Hz, H_{2eq}), 3.84 (dd, 1H, H_{2ax}), 3.36 (s, 3H, OCH_3), 1.48 (s, 3H, CH_3), 1.34 (s, 3H, CH_3); ($CDCl_3$, 50 MHz), δ 130.2-122.1 (C_{Ar}), 84.3 (C_3), 80.1 (C_4), 73.7, 72.5 (C_2, C_6), 65.2 (C_{10b}), 62.5 (OCH_3), 26.2 (CH_3), 24.8 (CH_3).
5. ($CDCl_3$, 500 MHz), δ 7.20-7.00 (m, 9H, H_{Ar}), 4.88 (dd, 1H, J_{3-4}= 6.0 Hz, J_{3-2ax}= 4.0 Hz, H_3), 4.82 (d, 1H, $J_{6,6'}$= 15.4 Hz, H_6), 4.75 (d, 1H, H_4), 4.68 (d, 1H, $H_{6'}$), 4.68 (d, 1H, J_{AB}= 12.0 Hz, CH_2Ph), 4.56 (d, 1H, CH_2Ph), 4.42 (s, 1H, H_{10b}), 3.92 (d, 1H, $J_{2eq-2ax}$= 10.5 Hz, H_{2eq}), 3.85 (dd, 1H, H_{2ax}), 1.48 (s, 3H, CH_3), 1.44 (s, 3H, CH_3); ($CDCl_3$, 50 MHz), δ 134.3-124.9 (C_{Ar}), 112.4 (C_{4a}), 107.6 ($C_{isopropyliden}$), 84.4 (C_3), 80.2 (C_4), 72.9, 71.9, 70.8 (C_2, C_6, CH_2Ph), 62.5 (C_{10b}), 26.3 (CH_3), 25.0 (CH_3).

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