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Stereoselective Synthesis of Nucleosides by Metallocene-Promoted Activation of Glycosyl Fluorides

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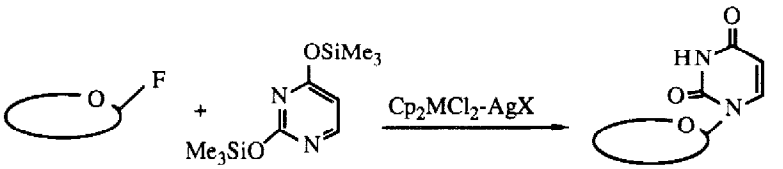
***Abstracts**: The Cp_2MCl_2-AgX (M=Hf, Zr; X=ClO_4, OTf) mixture is very effective for the promotion of the coupling of glycosyl fluorides and bis(trimethylsilyl)uracil. The stereoselectivity of the reaction depends on the solvent employed. Application to the synthesis of 1-(3,4 -isopropylidene-2-fluoro-2-O-methyl-α-D-ribopentopyranosyl)uracil is described.*

Many efforts have been devoted during the last years to the synthesis of nucleoside analogues of potential antiviral and antibiotic activity; a plethora of glycosilation methods[1] have been developed with this goal. In this context, glycosyl fluorides,[2,3] after the pioneering work of Mukaiyama,[4] have gained wide application because of their stability, easy of handling and availability of specific activation methods. However, the methodology based on the use of glycosyl fluorides has mostly been addressed to the synthesis of O-glycosides, rather than N-glycosides such as nucleosides.[3d,5] Our recent finding that alkyl α-2-uloses react with DAST to give 1,2-difluoro carbohydrates[6] prompted us to explore the preparation of nucleosides starting from glycosyl fluorides, in search of an efficient control of the stereoselectivity for sugars with non-participating protection at 2-OH.

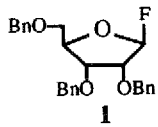
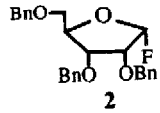
Previously, we have investigated the performance of the different methodologies[3] on standard substrates (ribofuranosyl fluorides **1** and **2**). Since in preliminary experiments the Suzuki method[4f-h] (see the following scheme) turned out to be more efficient and versatile in our hands, we describe first the results of glycosylation



of **1** and **2**[3g] with bis(trimethylsilyl)uracil, and then the application of the optimized protocol to obtain fluororibopyranosyl nucleosides **4** and **5** arising from **3**.

When tri-O-benzyl-D-ribofuranosyl fluoride was allowed to react with bis(trimethylsilyl)uracil in the presence of Cp_2MCl_2-AgX (Table 1) the desired nucleoside was obtained in aceptable to good yields. Similar results were obtained starting either from the α or from the ß (**1** and **2**, respectively) isomer in accordance with an ionic mechanism. The Hf based activators were more active than the Zr ones. The best results were obtained using Cp_2HfCl_2-AgOTf in benzene as the solvent, giving the ß isomer with a high stereoselectivity, which depends principally on the solvent used, having the temperature a small influence. This fact is remarkable considering the non-participating character of the benzyloxy groups.

Table 1. Cp_2MCl_2-AgX (M=Hf, Zr; X=ClO_4, TfO) promoted Glycosylation of Glycosyl Fluorides with Bis-(trimethylsilyl)uracil.[a]

Run	glycosyl fluoride	Activator	Solvent[b]	t	Yield	α/ß[c]
1	 **1**	Cp_2ZrCl_2-$AgClO_4$	CH_2Cl_2	24 h	65	32/68
2		Cp_2HfCl_2-$AgClO_4$	CH_2Cl_2[d]	24 h	82	45/55
3		Cp_2HfCl_2-$AgClO_4$	benzene	40 h	65	8/92
4		Cp_2HfCl_2-AgOTf	benzene	5 h	79	5/95
5	 **2**	Cp_2HfCl_2-$AgClO_4$	CH_2Cl_2	24 h	68	43/57

a) 0.1 mmol of substrate in 1 ml of solvent. Glycosyl fluoride/silyluracil/metallocene/silver salt ratio = 1/2/1/2

b) Reactions were carried out at -50 °C---rt in CH_2Cl_2, and at r.t. when the solvent was benzene.

c) Determined by ^1H NMR (300 MHz) spectroscopy.

d) When the reaction starts at r.t., the ratio α/ß is similar.

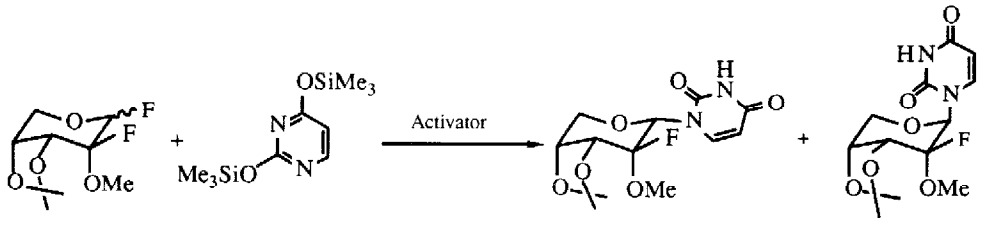
The reaction worked better starting at -50 °C, except when benzene was used as the solvent. Although significant amounts of product were obtained in the first 3-4 hours at room temperature, the reaction was left for 24 hours since this led to a slight improvement in the yield. When protecting groups Ac or Bz were used, no reaction was observed.

This procedure was applied to the glycosylation of 3,4-isopropylidene-2-fluoro-2-O-methyl-D-ribo-pentopyransyl fluoride (**3**), which was obtained as an inseparable anomeric mixture.[6] Reaction of **4** with bis(trimethylsilyl)uracil gave the nucleosides in good yields (Table 2). Only compounds **4** and **5** were obtained, i.e., both the fluorine and methoxy groups at position 2 were maintained, showing that F-1 reacts selectively in spite of the similar "situation" of F-1 and F-2.

Compound **4**, the equatorial isomer (as for **1** and **2**), was principally obtained, Cp_2HfCl_2-AgOTf in

benzene as the solvent also being the conditions of choice in this case. When the reaction was carried out in benzene heated to reflux decomposition was observed. The use of CH_3CN as the solvent increased the ratio of compound **5**.

Table 2: Cp_2MCl_2-AgX (M=Hf, Zr; X=ClO_4, TfO) Promoted Glycosylation of **3** with Bis-(trimethylsilyl)uracil.[a]



3 **4** **5**

Run	Activator	Solvent	Conditions[b]	Yield(%)	4/5[c]
1	Cp_2ZrCl_2-$AgClO_4$	CH_2Cl_2	-50°C---rt, 24 h	61	87/13
2	Cp_2ZrCl_2-AgOTf	benzene	rt, 24 h	53	87/13
3	Cp_2HfCl_2-$AgClO_4$	CH_2Cl_2	-50°C---rt, 24 h	87	82/18
4	Cp_2HfCl_2-$AgClO_4$	CH_2Cl_2	rt, 24 h	55	79/21
5	Cp_2HfCl_2-$AgClO_4$	CH_3CN	-50°C---rt, 24 h	72	57/43
6	Cp_2HfCl_2-$AgClO_4$	benzene	rt, 48 h	36	91/9
7	Cp_2HfCl_2-AgOTf	benzene	rt, 24 h	85	87/13

a) Glycosyl fluoride/silyluracil/metallocene/silver salt ratio = 1/2/1/2

b) Significant amounts of nucleoside were detected after 3-4 hours at r.t.

c) Determined by ^1H NMR (300 MHz) spectroscopy.

Compounds **4** and **5** were characterized spectroscopically.[7] The keys of the structural determination were: the absence of $^1J_{H,F}$ (it would have been present if glycosylation had taken place at position 2), the δ values of H-1 and C-1, and the $^3J_{H1,F}$ (which differentiates between **4** and **5**).

In summary, nucleosides can be prepared in good yields with high stereselectivity by activation of glycosyl fluorides with Cp_2HfCl_2-AgOTf, in benzene as the solvent. This methodology permits the direct and selective glycosylation of polyfluorinated carbohydrates.

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7. Compound **4**: white solid; m. p.= 183-185 °C; α_D= +53.2 (c=0.74, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MH) δ 9.70 (1H, NH); 7.52 (1H, dd, H-6, $J_{5,6}$=8 Hz, $J_{6,F}$=1.6 Hz); 5.79 (1H, dd, H-5, $J_{5,F}$=1 Hz); 5.69 (1H, d, H-1', $J_{1',F}$=13.2 Hz); 4.88 (1H, m, H-4'); 4.75 (1H, dd, H-3', $J_{3',4'}$=6.6 Hz, $J_{3',F}$=13 Hz); 4.24-4.21(2H, m, H-5'), 3.45 (3H, s, OMe); 1.57(3H, s, Me) 1.39 (3H, s, Me). ^{19}F (188 MHz, $CDCl_3$, ref. $CFCl_3$) δ -127.77 (t). ^{13}C ($CDCl_3$, 50.2 MHz) δ 163.5 (C-4); 151.7 (C-2); 140.4 (d , C-6, $J_{6,F}$=5.5 Hz); 116.4 ; 113.6 (d, C-2', $J_{2',F}$=246.9); 103.0 (C-5); 84.5 (d, C-1', $J_{1',F}$=27.3 Hz); 81.6 (d, C-3', $J_{3',F}$=21.5 Hz); 78.2 (C-4'); 72.4 (C-5'); 57.3 (OMe); 25.7; 25.3.
Compound **5**: ^1H NMR ($CDCl_3$, 200 MH) δ 8.86 (1H, NH); 7.54 (1H, dd, H-6, $J_{5,6}$=8.3 Hz, $J_{6,F}$=1 Hz); 5.81 (1H, d, H-1', $J_{1',F}$=7 Hz) ; 5.77 (1H, dd, H-5, $J_{5,F}$=1.8 Hz); 4.87-4.75 (2H, m, H-3', H-4'); 4.31-4.29 (2H, m, H-5); 3.44 (3H, s, OMe); 1.52 (3H, s, Me); 1.35 (3H, s, Me). ^{19}F (188 MHz, $CDCl_3$, ref. $CFCl_3$) δ -124.3 (dd). ^{13}C ($CDCl_3$, 50.2 MHz) δ 163.7 (C-4) 140.6 (C-6) ; 116.1 ;102.7 (C-5); 83.3 (d, C-1', $J_{1',F}$=35.2 Hz); 81.0 (d, C-3', $J_{3',F}$=20.8); 76.7 (C-4'); 73.0 (C-5'); 57.1 (OMe); 25.6, 25.3 (Me).

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