Organofluorine Compounds and Fluorinating Agents; 18:[1] Trifluoromethylzinc Bromide as a Reagent for the Preparation of Glycosyl Fluorides

Ralf Miethchen,* Christian Hager, Martin Hein

Department of Organic Chemistry, University of Rostock, Buchbinderstraße 9, D-18051 Rostock, Germany

Fax: +49(381)4981763; E-mail: ralf.miethchen@chemie.uni-rostock.de

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Dedicated to Prof. Dr. H. Bürger on the occasion of his 60th birthday

Trifluoromethylzinc bromide was used to prepare the corresponding glycosyl fluorides from the peracetylated α-pyranosyl bromides of D-glucose **1**, D-galactose **3**, D-mannose **5**, D-lyxose **7**, and L-rhamnose **9**, respectively, in good yields. D-Glucopyranosyl bromide **1** and the D-galactopyranosyl bromide **3**, exclusively delivered the corresponding β-D-glycosyl fluorides **2β** and **4β**. The other bromides **5**, **7** and **9** formed mixtures of anomeric fluorides (**6α/6β**, **8α/8β**, **10α/10β**). Similarily, the anomeric OH-groups of the D-glycopyranoses **11**, **12**, **13**, **15**, **17** could be substituted by fluoride using trifluoromethylzinc bromide/titanium tetrafluoride. In all cases mixtures of anomeric fluorides **2α/2β**, **6α/6β**, **14α/14β**, **16α/16β**, and **18α/18β** were obtained.

Glycosyl fluorides have become important in glycosylation reactions during the last decade[2-7] due to their enhanced stability[8,9] over other glycosyl halides and the possibility of their mild activation. Usually the activation is carried out with Lewis acids, e.g. BF_3,[5] $AgClO_4/TiF_4$[4] or $AgClO_4/SnCl_2$.[2a] Recently, rare earth salts were reported to be suitable catalysts in glycosylations with glycosyl fluorides.[10]

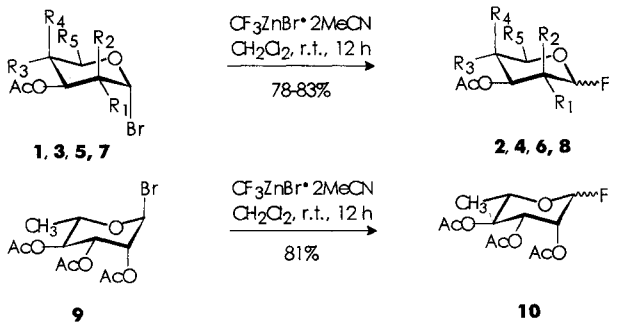
Various reagents and methods are known to introduce fluorine into the glycosidic position of sugar molecules.[11-14] Only a few of them allow the stereospecific synthesis of kinetically favoured β-D-glycosyl fluorides. Thus, good β-selectivities were achieved by nucleophilic substitutions of α-bromides with AgF,[11,15,16] KHF_2,[17] $Et_3N \cdot 3HF$[18] or ZnF_2.[19]

We used a new reagent $CF_3ZnBr \cdot 2CH_3CN$, originally introduced for difluoromethylation reactions.[20,21] It allowed the stereospecific synthesis of β-D-glycosyl fluorides, starting from glycosyl bromides or 1-OH-sugars, respectively. Trifluoromethylzinc bromide is easy to handle and is easily accessible using the convenient procedure of Naumann et al.[22]

$$CF_3ZnBr \cdot 2MeCN \rightleftharpoons "[CF_2ZnBr \cdot 2MeCN]^{\oplus} F^{\ominus}"$$

Scheme 1

Naumann et al.[23] postulated for trifluoromethylzinc bromide an equilibrium as shown in Scheme 1. Based on this, the reagent should also be applicable as a nucleophilic fluorinating agent. We investigated the reactions of the glycosyl bromides **1**, **3**, **5**, **7** and **9** with trifluoromethylzinc bromide ($CF_3ZnBr \cdot 2CH_3CN$) in dichloromethane at room temperature (Scheme 2). The corresponding glycosyl fluorides **2β**, **4β**, **6α/6β**, **8α/8β**, and **10α/10β** were formed in yields of about 80%. As expected, the 1,2-*trans*-arranged glycosyl fluorides were the predominantly formed products in all cases. This resulted from a pathway proceeding via a cyclic acyloxonium ion formed by the neighbouring group participation of the acetyl group in the 2-position.[24] A direct substitution of bromide by fluoride under inversion of the configuration at the C-atom 1 (S_N2 type reaction) could also occur at a minor rate. This is supported by the observation that small amounts of the corresponding β-glycosyl fluorides **6β** and **10β** were formed besides the major products **6α** and **10α** from the mannosyl bromide **5** and the L-rhamnosyl bromide **9**, respectively, whereas the gluco- and galactosyl bromides **1** and **3** exclusively yielded β-fluorides. The formation of about 28% 2,3,4-tri-*O*-acetyl-β-D-lyxopyranosyl fluoride (**8β**) from the bromide **7** could be explained by an increased conformational flexibility of the pentopyranose ring[25] which presumably causes a decrease in the activation energy for an S_N2 related transition state.

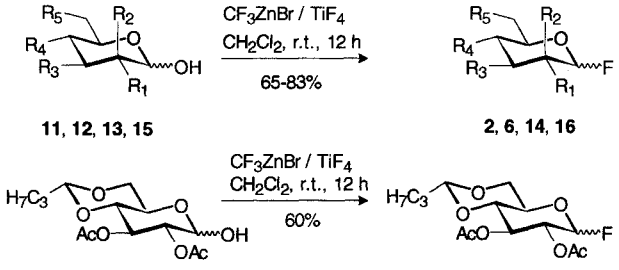


	R_1	R_2	R_3	R_4	R_5
1, 2β	OAc	H	OAc	H	CH_2OAc
3, 4β	OAc	H	H	OAc	CH_2OAc
5, 6β/6α	H	OAc	OAc	H	CH_2OAc
7, 8β/8α	H	OAc	OAc	H	H

Scheme 2

In a second experimental series we investigated the substitution of glycosidic OH-groups by fluoride. Attempts to use trifluoromethylzinc bromide under the same conditions as described for reactions with glycosyl bromides gave very low conversions. However, good results could be achieved, when the reaction was catalysed by TiF_4. The derivatives 2,3,4,6-tetra-*O*-acetyl-D-glucopyranose (**11**), 2,3,4,6-tetra-*O*-acetyl-D-mannopyranose (**12**), 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**13**), 3,4,6-tri-*O*-acetyl-2-deoxy-D-glucopyranose (**15**), and 2,3-di-*O*-acetyl-4,6-*O*-butylidene-D-glucopyranose (**17**) treated with

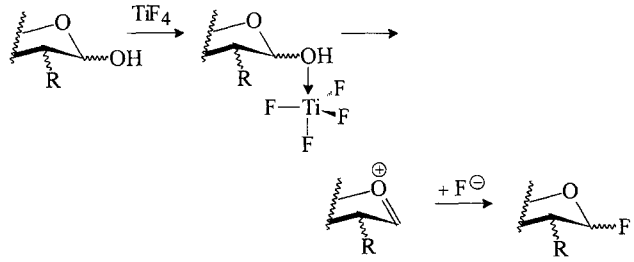
$CF_3ZnBr \cdot 2CH_3CN$ and TiF_4 in dichloromethane at room temperature gave the corresponding glycosyl fluorides **2**, **6**, **14**, **16**, and **18** in moderate to good yields (Scheme 3). To achieve such results, a larger excess of trifluoromethylzinc bromide is necessary as compared to the corresponding reactions of the glycosyl bromides.



	R_1	R_2	R_3	R_4	R_5
11, 2β/2α	OAc	H	OAc	OAc	OAc
12, 6β/6α	H	OAc	OAc	OAc	OAc
13, 14β/14α	OBn	H	OBn	OBn	OBn
15, 16β/16α	H	H	OAc	OAc	OAc

Scheme 3

In this procedure TiF_4 catalyses the OH–F-substitution (Scheme 4). The formation of α-glycosyl fluorides is stimulated by this Lewis acid as could be shown by a control experiment. Thus, pure 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl fluoride (**2**β) treated with $CF_3ZnBr \cdot 2CH_3CN$/TiF_4 under analogous reaction conditions gave nearly the same ratio of the anomeric fluorides **2**α/**2**β as the hydroxy-derivative **11**. Consequently, the formation of the α-glycosyl fluorides **2**α, **6**α, **14**α, **16**α and **18**α is caused by TiF_4-catalysis.



Scheme 4

It is noticeable that *O*-difluoromethylated derivatives of the pyranoses **11**, **12**, **13**, **15**, and **17** were only observed as byproducts. In contrast, carbohydrates containing free nonglycosidic OH-groups react with $CF_3ZnBr \cdot 2CH_3CN$ giving the corresponding *O*-difluoromethyl ethers[21] as major products.

Melting points were measured with a polarisation microscope (Leitz Laborlux 12 Pol with Mettler hot stage FP90). NMR spectra were recorded with a Bruker AC-250 spectrometer [solvent: $CDCl_3$; the signals are referenced to TMS (^1H and ^{13}C NMR), $CFCl_3$ (^{19}F NMR)]. Optical rotations were measured on a POLAR Lμ P-polarimeter (IBZ Meßtechnik). TLC was performed on silica gel coated foil (silica gel 60 F_{254} Fa. Merck). Preparative column chromatography was performed with silica gel 60 (63-200 μm, Fa. Merck), for solvent systems see procedures.

Preparation of source materials – The glycosyl bromides **1**, **3**, **5**, **7**, and **9** were prepared using HBr/HOAc according to the procedure reported in ref. 26. 4,6-*O*-Butylidene-D-glucopyranose was prepared as described in ref. 27. For all acylations the Ac_2O/pyridine system described in ref. 28 was used. 1-*O*-Deacylation of peracetylated pyranoses and 4,6-*O*-butylidene-1,2,3-tri-*O*-acetyl-α-D-glucopyranose with gaseous ammonia forming the 1-OH-sugars **11**, **12**, **15**, and **17** was performed according to ref. 29. Methyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside **(13)** was prepared as described in ref. 30. Cleavage of the anomeric methoxy group by trifluoromethanesulfonic acid was performed according to ref. 31.

Glycosyl Fluorides with Trifluoromethylzinc Bromide; General Procedures:

Method A (from glycosyl bromides): Glycosyl bromide **1**, **3**, **5**, **7**, and **9**, (3.4 mmol) respectively, trifluoromethylzinc bromide (1.15 g, 5.4 mmol),[22] molecular sieves (3 Å) (0.4 g) and anhyd CH_2Cl_2 (40 mL) were placed in a polyethylene flask. After stirring for 12 h at r.t., the mixture was agitated with sat. aq $NaHCO_3$ solution (20 mL) and filtered. Subsequently, the organic phase was separated, washed with H_2O (2 × 10 mL), dried (Na_2SO_4), and the solvent was evaporated under reduced pressure. The yellowish syrupy residue was purified by column chromatography; the major diastereomer could be obtained in pure form.

Glycosyl bromide	Glycosyl fluoride	Yield (%)	α/β-ratio[a]	Eluent toluene/EtOAc v/v
1	**2**β	83	only β	9 : 1
3	**4**β	82	only β	9 : 1
5	**6**α/**6**β	80	96.5/3.5[b]	9 : 1
7	**8**α/**8**β	78	71.5/28.5	9 : 1
9	**10**α/**10**β	81	98.0/2.0[c]	15 : 1

[a] Determined by ^1H NMR spectroscopy.
[b] ^1H, ^{13}C, ^{19}F NMR data of **6**β.[32a]
[c] ^1H and ^{13}C NMR data of **10**β.[18b]

*2,3,4-Tri-O-acetyl-α-D-lyxopyranosyl Fluoride (**8**α):*
$^{13}C\{^1H\}$ NMR (62.9 MHz, $CDCl_3$): δ = 169.8, 169.5, 169.5 (3 acetyl-CO), 105.0 (d, $^1J_{C\text{-}1/F} \approx 222.5$, C-1), 67.8 (d, $^2J_{C\text{-}2/F} \approx 39.3$, C-2), 68.7 (C-3), 65.7 (C-4), 61.4 (d, $^3J_{C\text{-}5/F} \approx 2.3$, C-5), 20.6, 20.5 (3 acetyl-CH_3).

*2,3,4-Tri-O-acetyl-β-D-lyxopyranosyl Fluoride (**8**β):*
^1H NMR (250 MHz, $CDCl_3$): δ = 5.58 (dd, 1 H, $^3J_{1,2} \approx 1.7$ Hz, $^2J_{1/F} \approx 47.2$ Hz, 1-H).
$^{13}C\{^1H\}$ NMR (62.9 MHz, $CDCl_3$): δ = 103.7 (d, $^1J_{C\text{-}1/F} \approx$ 233.1 Hz, C-1).
$^{19}F\{^1H\}$ NMR (235.5 MHz, $CDCl_3$): δ = −149.0.

*2,3,4-Tri-O-acetyl-β-L-rhamnopyranosyl Fluoride (**10**β):*
$^{19}F\{^1H\}$ NMR (235.5 MHz, $CDCl_3$): δ = −144.3.

Method B (from pyranoses): In a polyethylene flask 3.4 mmol of the corresponding 1-hydroxy sugar **11**, **12**, **13**, **15**, and **17**, respectively, trifluoromethylzinc bromide (2.9 g, 13.6 mmol),[22] molecular sieves (3 Å) (0.4 g), anhyd CH_2Cl_2 (40 mL), and TiF_4 (0.05 g, 0.4 mmol) were mixed and the mixture was stirred for 12 h at r.t. The workup procedure was the same as described for Method A.

Pyranose	Glycosyl fluoride	Yield (%)	α/β-ratio	Eluent toluene/EtOAc v/v
11	**2α/2β**	83	40.0/60.0	9 : 1
12	**6α/6β**	67	94.0/6.0[a]	9 : 1
13	**14α/14β**	65	91.0/9.0[b]	30 : 1
15	**16α/16β**	75	97.0/3.0[c]	9 : 1
17	**18α/18β**[d]	60	38.0/62.0	20 : 1

[a] NMR data of **6β**.[32a]
[b] ^1H, ^{13}C, ^{19}F NMR data of **14β**.[2a,32b]
[c] ^1H, ^{13}C, ^{19}F NMR data of **16β**.[15,32c]
[d] Not separated by column chromatography.

*2,3-Di-O-acetyl-4,6-O-butylidene-α-D-glucopyranosyl Fluoride (**18α**):*
$^{19}F\{^1H\}$ NMR (235.5 MHz, $CDCl_3$): $\delta = -147.1$.
*2,3-Di-O-acetyl-4,6-O-butylidene-β-D-glucopyranosyl Fluoride (**18β**):*
$^{19}F\{^1H\}$ NMR (235.5 MHz, $CDCl_3$): $\delta = -133.6$.

Table. Physical Properties of the Prepared Glycosyl Fluorides

Compound	mp/°C (solvent) (Lit. value)	$[\alpha]_D^{20}$ in $CHCl_3$ (Lit. value)	NMR data ^1H	^{13}C	^{19}F
2α	107–109 (EtOH) (105–107[33])	+89.6, $c = 1.10$ (+91.3[33])	34	34	34
2β	85–87 (EtOH) (78–79[18a])	+18.7, $c = 1.09$ (+20.0[18a])	34	34	34
4β	102–103.5 (toluene/heptane) (99–100[18a])	+12.1, $c = 1.06$ (+17.6[18a])	34	34	34
6α	67–68 (EtOH) (68–69[35])	+22.0, $c = 1.68$ (+21.8[35])	34	34	34
8α	88–89 (EtOH) (85–87[36])	−10.4, $c = 1.14$ (−15.0[37])	34	b	34
10α	syrup	−25.3, $c = 1.34$ (−30.0[38])	34	34	34
16α	73–74 (EtOH) (74[39])	+73.5, $c = 1.0$ (+73.9[39])	15,39	15	15,39
14α	69–71 (Et_2O) (68–69[40])	+9.3, $c = 1.12$ (+8.3[40])	34,40	40	34,40
18α	syrup	–	41	41	b
18β	syrup	–	41	41	b

[a] 22°C.
[b] NMR data see experimental part.

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