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Condensation of 1-Fluorofuranoses and Silylated Nucleobases Catalyzed by Tetrafluorosilane#

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The title reaction provides a generally useful tool for nucleoside synthesis. The stereoselectivities are highly influenced by the fluoride substrates, and steric course of the reaction of O-benzylated ribofuranosyl fluoride is solvent dependent.

The recent discovery that tetrafluorosilane (SiF_4) serves as an excellent catalyst for O-glycosylation reaction using protected 1-fluoroglucose[1] prompted us to extend the method to nucleoside synthesis.[2,3]

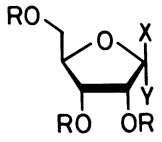
The starting 1-fluorofuranoses possessing appropriate protective groups have been prepared by treatment of corresponding acetates or free sugars with 50% HF in pyridine.[4] When a mixture of the fluoride (1-Fur-F) and a silylated uracil or adenine derivative ($B\text{-}[Si(CH_3)_3]_n$)[5] was treated with 10—30 mol% of SiF_4 and then with aqueous $NaHCO_3$, the corresponding nucleosides were obtained in good yields. This method finds wide applicability and a variety of sugars and nucleobases are employable. Table 1 lists some examples.

$$\text{1-Fur-F} + B\text{-}[Si(CH_3)_3]_n \xrightarrow[\text{2. aq } NaHCO_3]{\text{1. cat } SiF_4} \text{1-Fur-B}$$

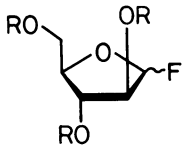
Fur = O-protected furanosyl group
B = pyrimidinyl or purinyl base

The reaction of ribofuranosyl fluoride **1** having "participating" benzoyloxy group at C-2 led solely to the β anomeric products (entries 1—4). Stereochemistry of the condensation with the fluoride **2** bearing "nonparticipating" benzyloxy group is influenced markedly by the nature of the solvents; the reaction in acetonitrile gave the β anomers preferentially (entries 5, 8, and 11), whereas low but opposite stereoselection was observed in dichloromethane or ether (entries 6, 7, 9, and 10).[6] This trend is not affected by stereochemistry of the starting fluorides. The kinetic stereoselection is conceivably made in the attack of the nucleophiles to the glycosyl cation/SiF_5^- ion-pair intermediates. The SiF_4-catalyzed condensation of arabinosyl fluorides (**3** and **4**) and uracil **6** afforded only α anomeric products regardless of the protective groups or reaction media

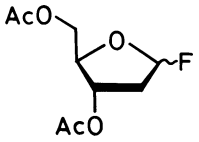
Dedicated to Professor Teruaki Mukaiyama on the occasion of his 60th birthday.



1α, R = Bz; X = H; Y = F
1β, R = Bz; X = F; Y = H
2α, R = Bn; X = H; Y = F
2β, R = Bn; X = F; Y = H



3, R = Bz
4, R = Bn



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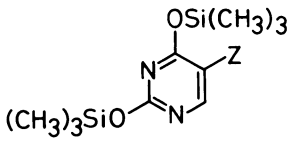
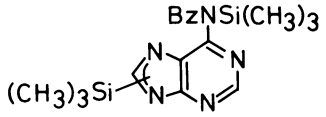


6, Z = H
7, Z = F



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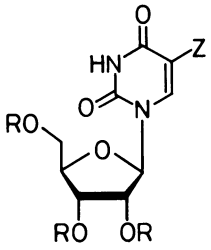
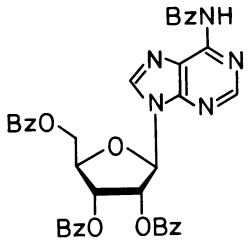


9, R = Bz; Z = H
10, R = Bz; Z = F
11, R = Bn; Z = H
12, R = Bn; Z = F



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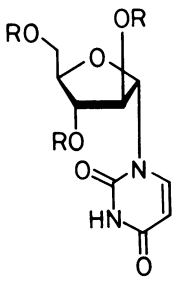
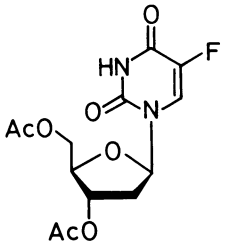


14, R = Bz
15, R = Bn



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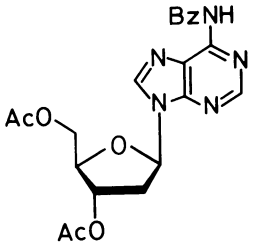

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Table 1. Synthesis of Nucleosides via Furanosyl Fluorides[a)]

Entry	Furanosyl fluoride	Nucleobase	Conditions			Product		
			SiF_4/mol%	Solvent	T/°C (time/h)	Number[b)]	Yield/%[c)]	α:β [d)]
1	**1**[e)]	**6**	20	CH_3CN	0 (2)	**9**	90	0:100[f)]
2	**1**[e)]	**6**	g)	CH_2Cl_2	0 (0.5)	**9**	88	0:100[f)]
3	**1**[e)]	**7**	20	CH_3CN	0 (2)	**10**	86	0:100[f)]
4	**1**[e)]	**8**	30	CH_3CN	0 (2)	**13**	82	0:100[f)]
5	**2α**	**6**	10	CH_3CN	0 (1)	**11**	85	16:84
6	**2α**	**6**	g)	CH_2Cl_2	0 (0.5)	**11**	80	60:40
7	**2α**	**6**	g)	$(C_2H_5)_2O$	0 (0.5)	**11**	82	55:45
8	**2β**	**6**	10	CH_3CN	0 (1)	**11**	84	18:82
9	**2β**	**6**	g)	CH_2Cl_2	0 (0.5)	**11**	84	68:32
10	**2β**	**6**	g)	$(C_2H_5)_2O$	0 (0.5)	**11**	78	60:40
11	**2β**	**7**	10	CH_3CN	0 (1)	**12**	70	16:84
12	**3**[e)]	**6**	20	CH_3CN	0 (2)	**14**	76	100:0[f)]
13	**4**[e)]	**6**	20	CH_3CN	0 (2)	**15**	78	100:0[f)]
14	**4**[e)]	**6**	g)	CH_2Cl_2	0 (2)	**15**	72	100:0[f)]
15	**5**[e)]	**7**	10	CH_3CN	-20 (2)	**16**	76	40:60
16	**5**[e)]	**8**	10	CH_3CN	-20 (2)	**17**	64	50:50

a) Reaction was carried out using 1.2—1.4 equiv. of the nucleobase to furanosyl fluoride under argon atomosphere. b) No positional isomers were obtained. c) Isolated yield. d) Determined by ^{1}H-NMR analysis. e) A 1:1 mixture of the α and β anomers. f) The minor isomer was not detectable by ^{1}H- (90 MHz) and ^{13}C-NMR analysis. g) Gaseous SiF_4 was introduced into the reaction mixture at 0 °C for 2 min.

(entries 12—14). 2-Deoxyribofuranosyl fluoride **5** reacted with bis-silylated uracil **7** or adenine derivative **8** to form mixtures of the α and β products (entries 15 and 16). The glycosylation of nucleobases is effected smoothly at or below 0 °C by using the reasonably stable fluoro sugars and a catalytic amount of SiF_4. Both pyrimidinyl and purinyl bases are equally employable. In place of SiF_4 other Lewis acids may be used but somewhat less satisfactorily.[7)] The present method is economical, operationally simple, and suitable for large-scale synthesis, and is thus not at all inferior to the well-known Vorbrüggen's silyl version of Hilbert-Johnson method (trialkyl triflate-promoted condensation of peracylated sugars and silylated nucleobases).[8,9)]

A typical procedure is illustrated as follows (entry 1 in Table 1). In a dry glass tube were placed 2,3,5-tri-O-benzoyl-D-ribofuranosyl fluoride **1** (529 mg, 1.14 mmol) and bis(trimethylsilyl)uracil **6** (359 mg, 1.40 mmol) in acetonitrile (2 mL). Then acetonitrile solution of SiF_4 (0.08 M, 2.9 mL, 0.23 mmol) was added at 0 °C, and the resulting mixture was stirred for 2 h at the same temperature and poured into a saturated $NaHCO_3$ solution. Extraction with ethyl acetate (50 mL x 2) was followed by washing of organic layer with a saturated $NaHCO_3$ solution (20

mL x 2) and brine (20 mL), drying over Na_2SO_4, and concentration. Chromatography on a silica-gel column (20 g, 1:2 hexane—ethyl acetate as an eluent) gave the uridine derivatives **9** (569 mg, 90%) as white crystals, mp 140—141.5 °C (lit[10] 138—140 °C).

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References

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2) Mukaiyama has used 1-fluorinated sugars in O-glycosylation aided by $AgClO_4$/$SnCl_2$. See: T. Mukaiyama, Y. Murai, and S. Shoda, Chem. Lett., 1981, 431; T. Mukaiyama, Y. Hashimoto, and S. Shoda, Chem. Lett., 1983, 935.
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6) For similar solvent dependency, see: ref. 1. An explanation was given in: R. Noyori, M. Hayashi, and S. Hashimoto, "Organosilicon and Bioorganosilicon Chemistry: Structure, Bonding, Reactivity and Synthetic Application," ed by H. Sakurai, Ellis Horwood, West Sussex (1985), pp. 213-218.
7) Use of larger amounts of the promotors is required to obtain high yields. Results of reaction **1** and **6**, giving **9**, in acetonitrile in the presence of various Lewis acids were: 50 mol% TMSOTf, 0 °C, 6 h, 87% yield; 50 mol% BF_3 etherate, 0 °C, 6 h, 85%; 100 mol% $SnCl_4$, 4 °C, 12 h, 88%; 100 mol% $AlCl_3$, 4 °C, 12 h, 78%. The $TiCl_4$ promoted reaction in 1,2-dichloroethane (100 mol% promotor, 4 °C, 12 h) gave **9** in 74%.
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