STEREOSELECTIVE SYNTHESIS OF α-RIBONUCLEOSIDES
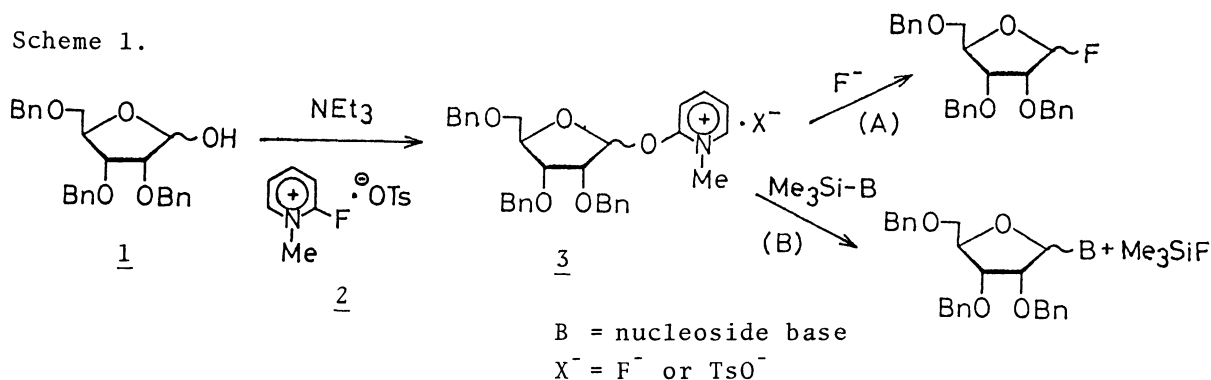## FROM 1-HYDROXY SUGARS BY USING 2-FLUOROPYRIDINIUM TOSYLATE

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A novel method for the preparation of α-ribonucleosides was
developed by the use of 2-fluoro-1-methylpyridinium tosylate as a
condensing reagent. Various α-ribonucleosides were synthesized
from 1-hydroxy sugars and trimethylsilylated nitrogen compounds,
such as nucleoside bases and azide, in good yields under mild
conditions.

In recent years, much attention has been given to biologically active 1',2'-
cis-nucleosides, which involve α-ribazole [a component of vitamin B_{12}, 5,6-di-
methyl-1-(α-D-ribofuranosyl)benzimidazole] and ara-A (9-β-D-arabinofuranosyl-
adenine). Concerning the N-glycosylation reactions directed toward the synthesis
of 1',2'-*cis*-nucleosides, there have been reported few general and useful
methods.[1] In this communication, we wish to report an efficient method for the
preparation of α-ribonucleosides starting from 1-hydroxyribofuranoses and
trimethylsilylated nucleoside bases by using 2-fluoropyridinium tosylate as a
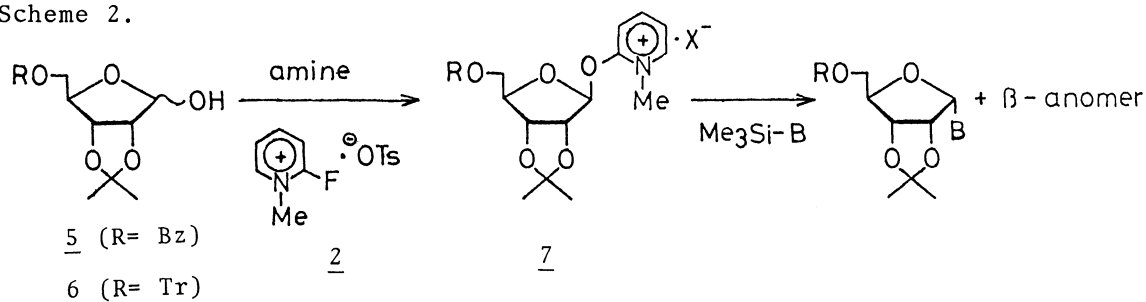condensing agent.[2]

It has already been found in our laboratory that the 2-fluoropyridinium salt
is a superior reagent for the convenient synthesis of glycosyl fluorides from 1-
hydroxy sugars[4] (Scheme 1, route A). Based on the results, it was postulated
that, when the intermediate 3 is more reactive toward a nucleoside base than the
fluoride ion under appropriate conditions, a N-glycosyl compound could be formed
as shown in Scheme 1 (route B).

Scheme 1.

B = nucleoside base
X⁻ = F⁻ or TsO⁻

At the first stage, the reaction of 2,3,5-tri-O-benzyl-D-ribofuranose[5] (1)
and 1-trimethylsilylbenzimidazole (4) was examined using 2-fluoro-1-methyl-
pyridinium tosylate[6] (2) as a condensing reagent. Fortunately, the corresponding
nucleoside with α-configuration was predominantly obtained (α/β = 76/24). To
achieve higher stereoselectivity, we next screened the reaction conditions using
various 1-hydroxy sugars taking 1-trimethylsilylbenzimidazole (4) as a model
silylated nucleoside base. The result shows that the reaction of 5-O-benzoyl-2,3-
O-isopropylidene-D-ribofuranose[7] (5) or 2,3-O-isopropylidene-5-O-triphenylmethyl-
D-ribofuranose[8] (6) with 4 in the presence of 1-ethylpiperidine or N-ethyldi-
isopropylamine gave the best result (Scheme 2).
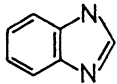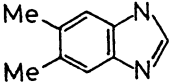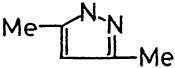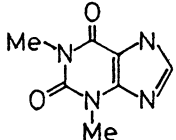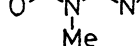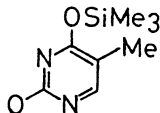
Scheme 2.

5 (R= Bz)

6 (R= Tr)

2

7

The following is a typical procedure for the preparation of 1-(5-O-benzoyl-
2,3-O-isopropylidene-α-D-ribofuranosyl)benzimidazole: To a stirred suspension of
2-fluoropyridinium salt 2[6] (0.38 mmol) in dichloromethane (1 ml) was added a
dichloromethane solution (2 ml) of 5-O-benzoyl-2,3-O-isopropylidene-D-ribo-
furanose[7] (5, 0.23 mmol) and N-ethyldiisopropylamine (0.51 mmol) at -30 °C and
the reaction mixture was stirred for 3 h with gradually warming to -5 °C. To this
yellowish solution was added a dichloromethane solution (2 ml) of 1-trimethyl-
silylbenzimidazole (4, 0.89 mmol). After the reaction was completed (0 °C, 1 d
then rt, 1 d), the solvent was evaporated in vacuo and the residue was applied
to silica gel column chromatography and 1-(5-O-benzoyl-2,3-O-isopropylidene-D-
ribofuranosyl)benzimidazole was isolated in 82% yield (α/β = 89/11).

In a similar manner, several α-ribonucleosides are prepared in good yields as
shown in Table 1.

In general, when 5-O-benzoyl-2,3-O-isopropylidene-D-ribofuranose[7] (5) was
employed as a 1-hydroxy sugar, the reaction proceeded more stereoselectively com-
pared with the similar reaction of 5-O-triphenylmethyl derivative 6.[8] It is
noted that, according to the present procedure, an α-ribazole derivative was
synthesized in high yield (entry 2), and also azide group could be smoothly intro-
duced to anomeric center of ribofuranose (entry 7). Based on low temperature [1]H
and ^{13}C NMR spectra of the intermediate 7 (R= Bz), essentially one anomer (β-form)
could be detected. It suggests that the intermediate 7 is selectively formed by
the reaction of 2-fluoropyridinium tosylate 2 with β-anomer of 1-hydroxy sugar,
which is in equilibrium with α-anomer. Desired α-ribonucleosides are considered

Table 1.   Synthesis of Ribonucleosides[a]

Entry	B of Me₃Si-B	Sugar	Yield /%	α / β
1		5	82	89 / 11 [b]
2		5	80	90 / 10
3		5	82	86 / 14 [b]
4		5	99	84 / 16
5		6	53	32 / 68 [9]
6		5	32	53 / 47
7	N₃	6	100	82 / 18 [10]
8		1	71	74 / 26 [c]
9		6	71	76 / 24 [d]

a) Reactions were carried out with 1-ethylpiperidine as a base,
   except for entries 1 and 3.   All products gave satisfactory NMR
   spectra.   The anomeric configuration of the products was deter-
   mined by NMR data[13] and physical constants.[1c,11,12]
b) N-Ethyldiisopropylamine was used as a base.
c) O-Glycosylation proceeded exclusively instead of the desired N-
   glycosylation.
d) The products are assigned to be N-glycosyl compounds by NMR data.

to be the products of S_N2 reaction with inversion of anomeric center of the inter-
mediate 7, while undesired β-isomers are possibly formed *via* S_N1 type reaction
path.   The predominant formation of β-anomer in the case of theophiline derivative
(entry 5) may due to insolubility of the corresponding anion of the silylated base

to the solvent, which makes S_N2 type reaction path unfavorable.

An attempt to obtain α-adenosine and an application of this method to the synthesis of 1',2'-cis-nucleosides containing arabinose are now in progress.

References

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   c) H. Tsutsumi, Y. Kawai, and Y. Ishido, Chem. Lett., 1978, 629; H. Tsutsumi, K. Okazaki, M. Asai, K. Itoh, F.-H. Kuan, and Y. Ishido, Nippon Kagaku Kaishi, 1982, 1682;

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2) We have already reported a synthesis of nucleosides using benzoxazolium salt,[3] however, according to this procedure, α-ribonucleosides can not be obtained because of the neighboring participation of 2-acyloxy group of 1-hydroxy sugar.

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4) T. Mukaiyama, Y. Hashimoto, and S. Shoda, Chem. Lett., 1983, 935.

5) R. Barker and H. G. Fletcher, Jr., J. Org. Chem., 26, 4605 (1961).

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7) This compound is synthesized by three steps procedure from D-ribono-1,4-lactone in 89% overall yield [(i) acetone, H^+ (ii) PhCOCl, pyridine (iii) bis-(1,2-dimethylpropyl)borane, THF].

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9) α-Anomer: mp 178-179 °C (MeOH) [lit,[1c] 174.5-175 °C (MeOH)]. β-Anomer: mp 259-262 °C (EtOH) [lit,[1c] 267-269 °C (EtOH)], $[\alpha]_D^{24.5}$ +13° (c 1.2, $CHCl_3$) [lit,[1c] $[\alpha]_D^{22}$ +20° (c 1.0, $CHCl_3$)].

10) α-Anomer: mp 105-106 °C (Et_2O - petroleum ether), $[\alpha]_D^{28}$ +9.6° (c 1.1, $CHCl_3$) [lit,[11] $[\alpha]_D$ +8° (c 1, $CHCl_3$)], IR (KBr) 2115 cm^{-1} (N_3) (lit,[11] 2135 cm^{-1}). β-Anomer: $[\alpha]_D^{18.5}$ -118° (c 1.0, $CHCl_3$) [lit,[12] $[\alpha]_D^{25}$ -98.0° (c 2.74, $CHCl_3$)], IR (neat) 2115 cm^{-1} (N_3) [lit,[12] ($CHCl_3$) 2113 cm^{-1}].

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