CHEMISTRY LETTERS, pp. 557 - 560, 1984.

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

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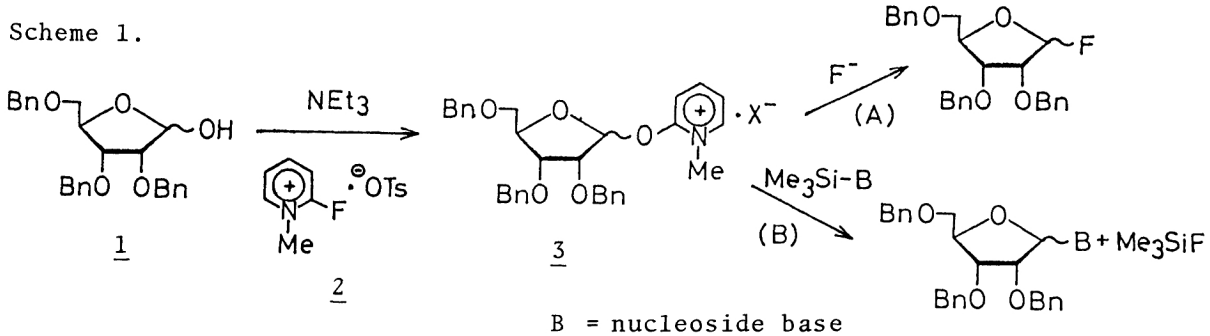
A novel method for the preparation of α-ribonucleosides was developed by the use of 2-fluoro-1-methylpyridinium tosylate as a condensing reagent. Various α-ribonucleosides were synthesized from 1-hydroxy sugars and trimethylsilylated nitrogen compounds, such as nucleoside bases and azide, in good yields 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-dimethyl-1-(α-D-ribofuranosyl)benzimidazole] and ara-A (9-β-D-arabinofuranosyladenine). 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]

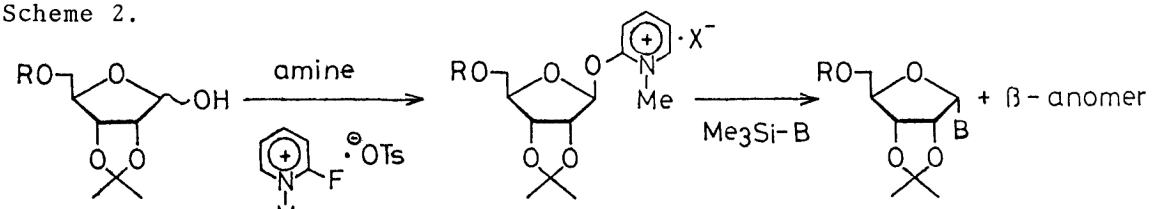
It has already been found in our laboratory that the 2-fluoropyridinium salt is a superior reagent for the convenient synthesis of glycosyl fluorides from 1-hydroxy sugars[4] (Scheme 1, route A). Based on the results, it was postulated that, when the intermediate 3 is more reactive toward a nucleoside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

Scheme 1.



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-methylpyridinium 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-ethyldiisopropylamine gave the best result (Scheme 2).

Scheme 2.



5 (R= Bz)

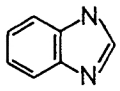
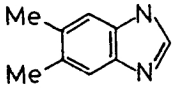
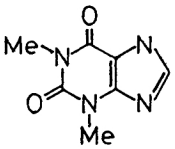
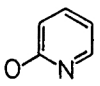
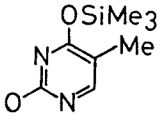
6 (R= Tr)

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-ribofuranose[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-trimethylsilylbenzimidazole (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 compared 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 introduced 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 Me_3Si-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	N_3	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 determined 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 intermediate 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

1) a) J. D. Stevens, R. K. Ness, and H. G. Fletcher, Jr., J. Org. Chem., 33, 1806 (1968), and the references cited therein. See also: H. G. Fletcher, Jr., Trans. N. Y. Acad. Sci., 30, 649 (1968);
b) Y. Furukawa, K. Imai, and M. Honjo, Tetrahedron Lett., 1968, 4655;
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;
d) F. Seela, D. Hasselmann, and H.-D. Winkeler, Justus Liebigs Ann. Chem., 1982, 499; F. Seela and H.-D. Winkeler, J. Org. Chem., 47, 226 (1982), and the references cited therein.

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).

6) T. Mukaiyama, Angew. Chem., Int. Ed. Engl., 18, 707 (1979).

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].

8) T. J. Cousineau and J. A. Secrist III, J. Org. Chem., 44, 4351 (1979).

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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(Received January 24, 1984)