Synthesis and Modification of β-*D*-Xylofuranosylnucleosides

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Abstract

Original reaction schemes for the synthesis of well-known anti-HIV preparations such as azidothymidine and 2′,3′-dideoxy-2′,3′-didehydrothymidine (D_4T) are presented. Potentialities of using the silyl-based method for the synthesis of glycosides of biologically active nitrogen-containing heterocycles are demonstrated.

Key words: β-*D*-xylofuranosilnucleosides, silyl method, *D*-xylose, thymine, uracil, azidothymidine, ellipticine, 6,7-difluoroquinolonecarbonic acid

INTRODUCTION

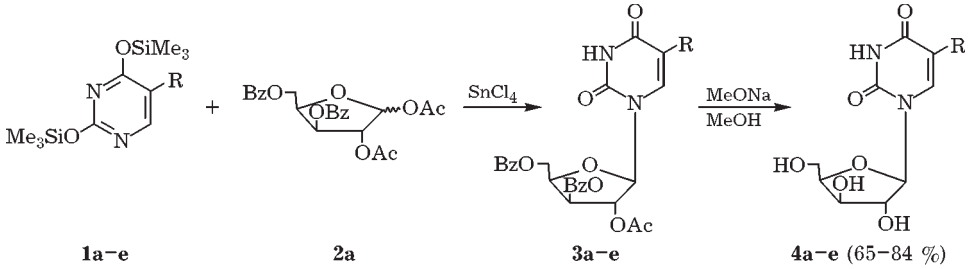
Synthetic analogues nucleosides find application in medicine as antiviral and antineoplastic preparations. For example, they are presented by anti-HIV preparations such as 3′-deoxy-3′-azidothymidine (AZT) and 2′,3′-dideoxy-2′,3′-didehydrothymidine (D_4T), anti-herpes preparations such as 5-bromovinyl-2′-deoxyuridine (BVDU), 9-(2-oxyethoxymethyl) guanosine (Acyclovir), antineoplastic preparations such as 1-β-*D*-arabinofuranosylcytosine (Cytarabin), *etc.*

In this paper we demonstrate the results of some our studies concerning the synthesis and modification of xylofuranosylnucleosides.

SYNTHESIS OF XYLOFURANOSYLNUCLEOSIDES

Nowadays the synthesis of нуклеозидов, as a rule, is carried out through a silyl method based on the interaction of silylated nucleic bases with the derivatives of monosaccharides in the presence of Lewis acids in an absolute solvent (acetonitrile, 1,2-dichloroethane, *etc.*) [1, 2].

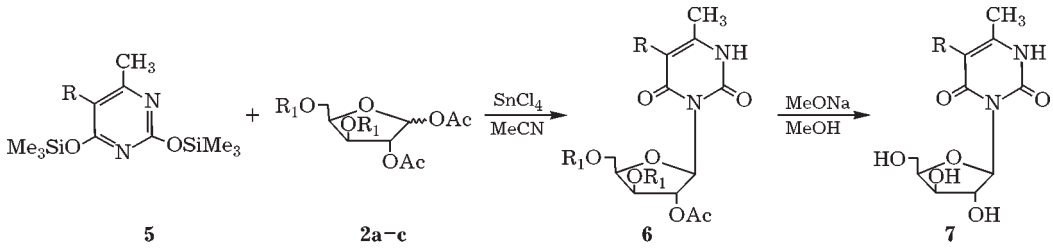
In the course of the condensation of silylated uracils **1a–e** with xylofuranose **2** in 1,2-dichloroethane (DCE) the only N-1-substituted nucleosides **3a–e** are formed with a high yield. By means of the removal of protective groups from compounds **3a–e** in 0.1 M MeONa solution in MeOH medium we obtained corresponding



1a–e **2a** **3a–e** **4a–e** (65–84 %)

1, **3**, **4** R = H (**a**), Me (**b**), F (**c**), Br (**d**), I (**e**)

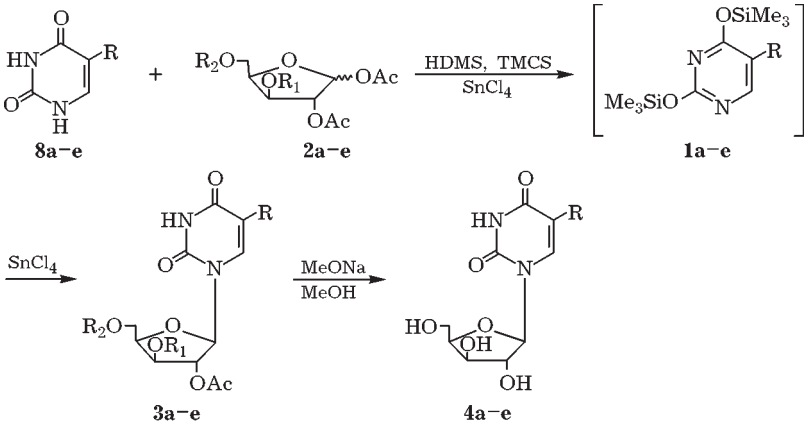
Scheme 1.



5 **2a–c** **6** **7**

R = H, OH; $R_1 = R_2$ = Bz (**a**); $R_1 = R_2$ = Ac (**b**); R_1 = Ac, R_2 = Bz (**c**).

Scheme 2.



8a–e **2a–e** **1a–e** **3a–e** **4a–e**

R = H (**a**), Me (**b**), F (**c**), Br (**d**), I (**e**); $R_1 = R_2$ = Bz (**a**); $R_1 = R_2$ = Ac (**b**).

Scheme 3.

N-1-nucleosides **4a–e.** It has been established that the nature of a solvent in the process of silylated uracils condensation influences insignificantly the yield of nucleosides expected to form, whereas $SnCl_4$ appeared the most efficient catalyst (Scheme 1).

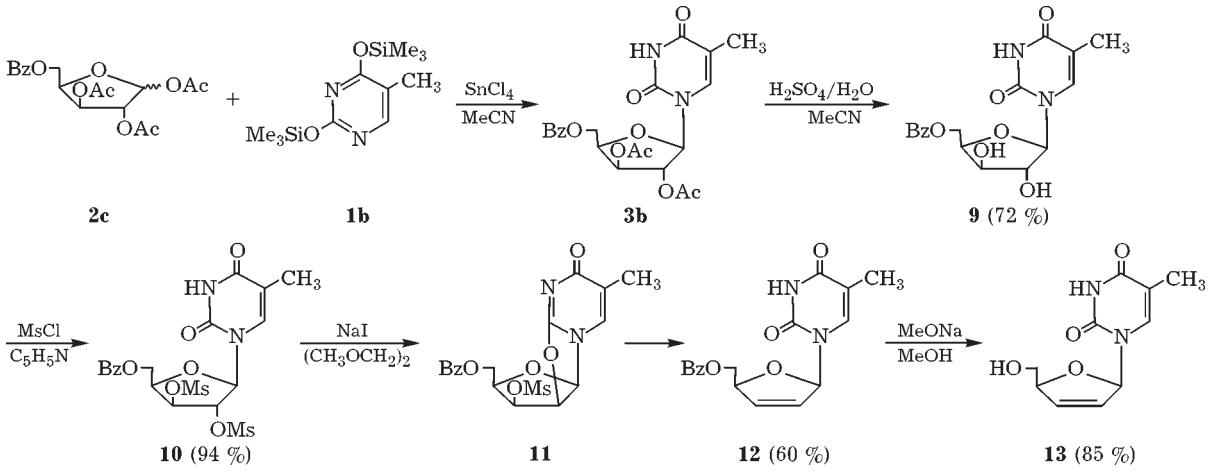
The methyl group at the position 6 of the uracil molecule displaces reaction towards the formation of N-3-nucleosides, which is observed for the condensation of silylated 6-methyluracil and 5-hydroxy-6- methyluracil (Scheme 2).

Another way to synthesize nucleosides consists in the direct condensation of uracil derivatives **8a–e** with xylofuranosides in the presence of hexamethyldisilazane (HMDS) and trimethylchlorosilane (TMCS) under the action of $SnCl_4$ in MeCN or 1,2-DCE solution according to the Vorbruggen method. To all appearance, the reaction proceeds through the stage of uracil silylation with the subsequent condensation of an intermediate silyl derivative with xilofuranose, which results in the formation of nucleosides **4a–e**. The yield of the compounds in this case appeared a little lower in comparison with the yield obtained with the use of the silyl method (Scheme 3).

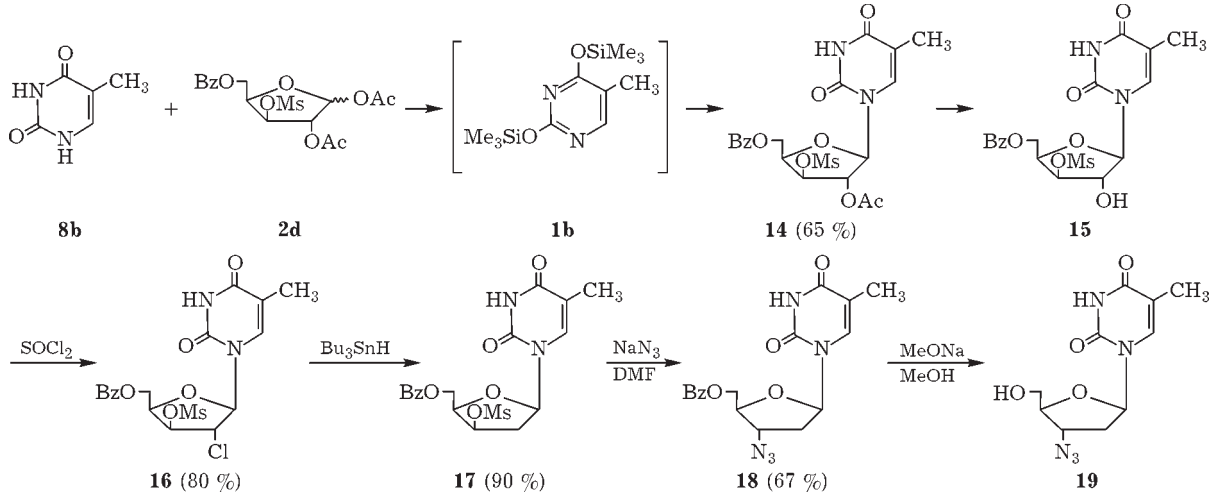
MODIFICATION OF THE CARBOHYDRATE FRAGMENT

Among the preparations used for HIV chemotherapy, compounds D_4T and AZT find application. The results of the studies concerning the synthesis of 2′,3′-unsaturated nucleosides have been used as the basis for the reaction scheme of D_4T obtaining we developed (the total yield of compound **19** amounted to 28 %) (Scheme 4) [3–9].

AZT is most widely used in AIDS chemotherapy. The method we have developed for its obtaining allows one to avoid any excess stages as well as to increase the total yield of the products [10, 11]. The total yield of target substance **19** according to the mentioned reaction scheme as calculated for *D*-xylose amounted to 21 % (Scheme 5).



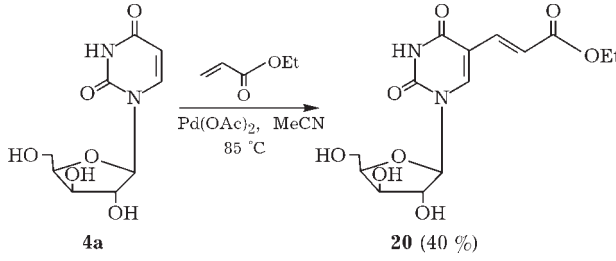
Scheme 4.



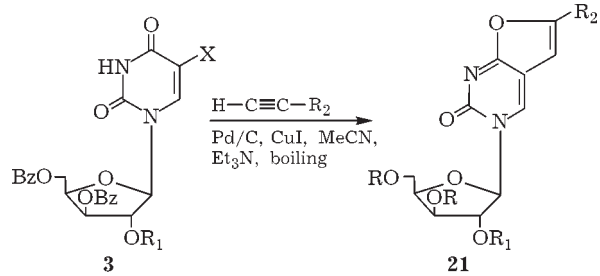
Scheme 5.

MODIFICATION OF THE AGLYCON FRAGMENT

One of the ways to synthesize modified nucleosides consists in the transformation of the aglycon part. The introduction of a substituent into the C-5 position of uracil via the oxidative addition of unsaturated compounds represents a promising approach to the modification of aglycon. We have studied the reactions between alkyl esters of unsaturated carbonic acids (acrylic, 5-hexenic and sorbic acids) and uracil-based nucleosides in the presence of palladium (II) acetate [12, 13]. The oxidative addition of unsaturated compounds to nucleosides was observed only with involving ethylacrylate in the reaction. Nucleoside **4a** boiling in MeCN medium with ethylacrylate in the presence of palladium (II) acetate results in the formation of product **20** (Scheme 6).

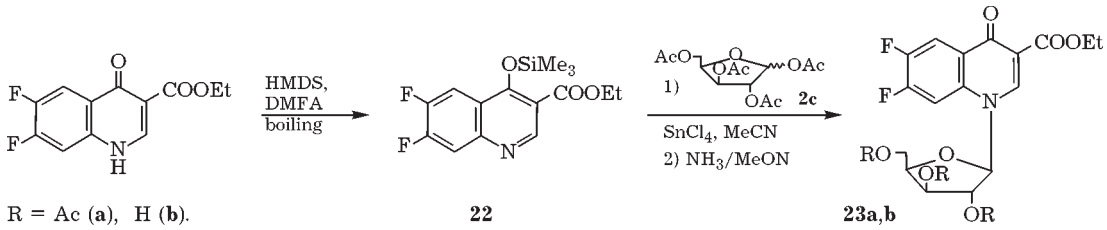


Scheme 6.



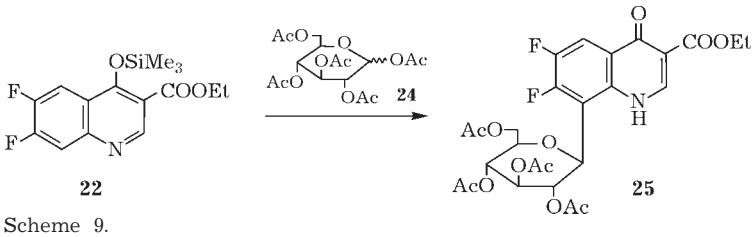
X = I, Br; R_1 = Ac, H; R = Bz, H; R_2 = Ph, $Me(CH_2)_7$, CH_2OH.

Scheme 7.



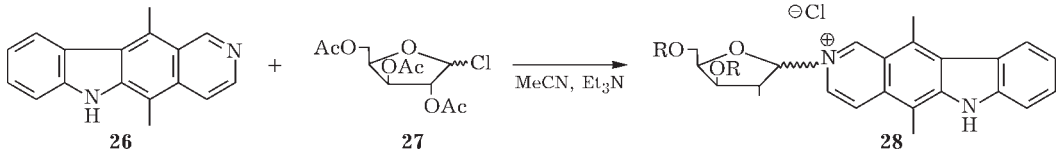
R = Ac (**a**), H (**b**). **22** **23a,b**

Scheme 8.



22 **24** **25**

Scheme 9.



26 **27** **28**

Scheme 10.

Under the conditions of heterogeneous catalysis on heating 5-halogenonucleosides **3** with 1-alkines in the presence of 10 % Pd/C and CuI in the TEA/MeCN mixture we have obtained furano[2,3-d] pyrimidene-2-ones **21** [14, 15] (Scheme 7).

The introduction of the carbohydrate fragment into biologically active heterocyclic compounds allows increasing their water-solubility and bioavailability. For this purpose we have investigated the glycosylation reaction of 6,7-difluoroquinolonecarbonic acid and antineoplastic alkaloid ellipticine [16, 17]. The reaction between silyl derivative **22** and xylofuranose **2c** results in the formation of N-glycoside **23**. The unblocking of the glycoside was carried out via its treatment with NH_3/MeOH (Scheme 8).

The fact that the reaction between siloxy-ether **22** with penta-O-acetyl-*D*-glucopyranose **24** proceeds as C-8-glycosylation has appeared unexpected (Scheme 9).

The glycosylation of ellipticine occurs due to the interaction between alkaloid **26** and 1-chloro-2,3,5-tri-O-acetyl-*D*-xylofuranose **27**. As a result, 2-N-glycoside **28** has been obtained with a quaternized pyridinium nitrogen atom of ellipticine (Scheme 10).

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