SciForum
Mol2Net

Fluorinated Nucleosides

Mohamed Ibrahim Elzagheid*
Chemical and Processing Engineering Technology Department (Industrial Chemistry), Jubail Industrial College, PO Box 10099, Jubail Industrial City 31961, Kingdom of Saudi Arabia
Email: elzagheid_m@jic.edu.sa, elzagheid66@yahoo.com

Published: 4 December 2015

Abstract: In this mini review the synthesis of base- and sugar-fluorinated nucleosides is discussed and the use of different fluorinating agents is briefly elaborated within the text. Introduction of fluorine substituent into pyrimidine and purine nucleosides has surely led to a change in the overall chemical behavior. In fact, there are many examples of the sugar fluorinated nucleosides that make a great impact on chemistry, biochemistry, and drug discovery.

Keywords: Nucleoside, fluorinated nucleosides, fluorinating agents.

Introduction

Chemists introduced fluoro group into sugars and nucleosides by different methods and this let for the formation of fluorine carbon bond. Incorporation of fluorine atom into nucleosides especially at the sugar moiety added interesting biological activities to the nucleosides. This is may be due to the electronegativity of fluorine and the strength of the carbon-fluorine bond. Fluorinated nucleosides exhibit interesting physical-chemical properties as nucleosides[1] or as monomers in oligonucleotide synthesis.[2] The synthesis of fluorinated nucleosides (**figure 1, 1-9**) can be achieved by selective fluorination of nucleosides or by glycosylation of nucleobases or fluoro-nucleobases with fluoro-sugar derivatives.[3-8]

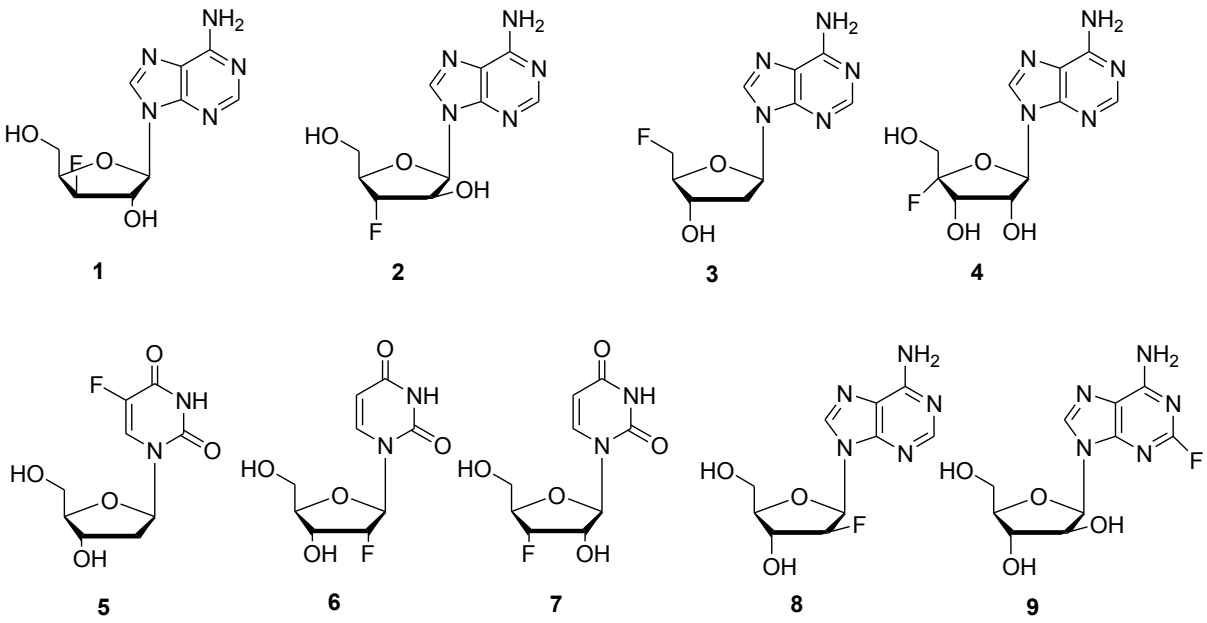
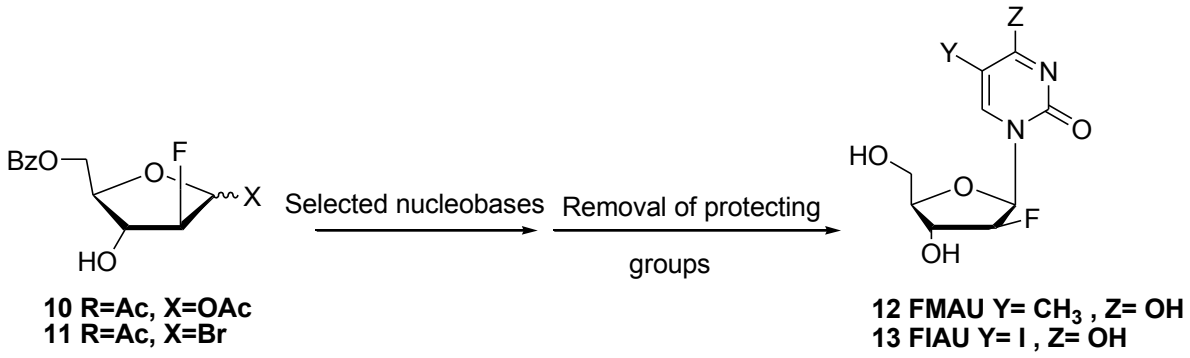


Figure 1

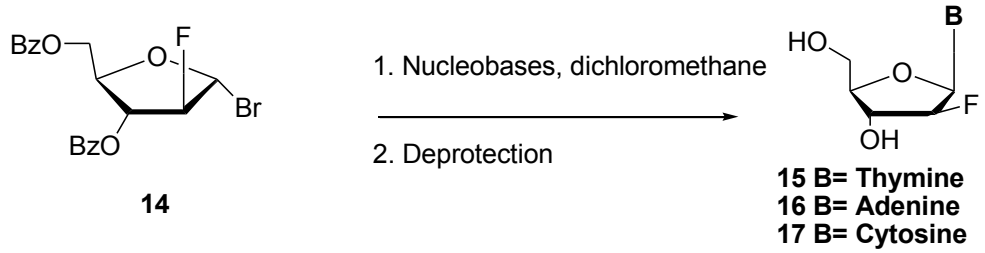
Synthesis of Modified Fluoronucleosides

Different methods were developed for the synthesis of 2'-fluornucleosides. Among those methods the one that was published by Watanabe *etal*.[9] This synthetic method involves the coupling of 2-deoxy-2-fluoro-D-arabinose **10** and 1-bromo-2-deoxy-2-fluoro-**D**-arabinose **11** with selected nucleobases to give fluoronucleosides **12** and **13** (**Scheme 1**).



Scheme 1

2'-Fluorinated nucleosides, namely 2'-deoxy-2'-fluoro arabinonucleosides (araF-nucleosides)[10,11] were used as building blocks for the synthesis of 2'-deoxy-2'-fluoro arabinonucleic acid (2'-F'ANA),[12-14] a very promising antisense oligonucleotides. Here the 2'-fluoro nucleosides were prepared via condensation of the silylated nucleic acids bases; silylated *N*-acetyl cytosine or silylated thymine or *N*-benzoylated adenine with 2-deoxy-2-fluoro-3, 5-di-O-benzoyl-α-**D**-arabinofuranosyl bromide **14**. Deprotection of the produced the desired nucleosides **15-17** in good yield (**Scheme 2**).

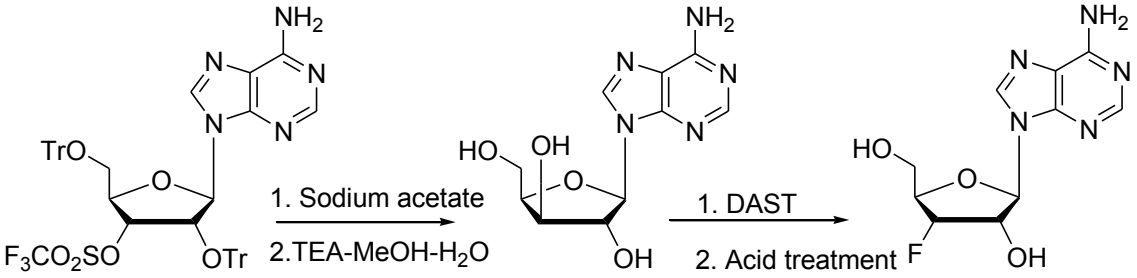


14

15 B= Thymine
16 B= Adenine
17 B= Cytosine

Scheme 2

Synthesis of 3'-fluorinatednucleosides has been reported by Hansske *et al*.[15] This involves the treatment of the nucleoside triflate **18** with sodium acetate followed by mild hydrolysis of the later nucleoside in triethylamine-methanol-water mixture gave nucleoside **19** in good yield. When nucleoside **19** was treated with DAST [(diethylaminosulfurtrifluoride, Et_2NSF_3] followed by acid treatment nucleoside **20** was obtained in good yield (**Scheme 3**).



18 **19** **20**

Scheme 3

Fluorinating Agents

Fluoride ion is the smallest anion with the largest negative charge density. In general it acts as a hydrogen-bond acceptor rather than as a nucleophilic agent. Depending on the reaction environment, the fluoride ion can act either as a poor nucleophile or as a good nucleophile. Activation of alcohols with good leaving groups, such as mesylate, tosylate or triflate; followed by a S_N2 substitution by a fluoride ion has become a standard method to replace OH with F. Fluorinating agents can be classified into nucleophilic reagents and electrophilic reagents. Fluorinating reagents (**Figure 2**) that are usually used for the fluorination of the hydroxyl groups in sugars or nucleosides are listed below:

i. **Pyridinium poly (hydrogen fluoride, PPHF or Py.nHF) - Olah's reagent**[16]

The Olah reagent is a nucleophilic fluorinating agent. It consists of a mixture of 70 % hydrogen fluoride and 30% pyridine. Secondary and tertiary alcohols can be converted to the corresponding fluorides by this reagent.

ii. **Diethylaminosulfur trifluoride, Et_2NSF_3- DAST reagent**

DAST was prepared by the reaction of SF_4 with diethylaminotrimethylsilane.[17]It is the most versatile reagent in nucleoside chemistry for a one-step exchange of the hydroxyl group by fluorine via S_N2 displacement. This reaction occurs with a complete inversion of configuration. It can replace primary, secondary and tertiary hydroxyl groups with fluorine in very good yields.

iii. **1-Chloromethyl-4-fluoro-1, 4-diazoniabicyclo [2.2.2] octane bis (tetrafluoroborate) Selectfluor reagent**

Selectfluor has much higher reactivity than NFSI. It is a stable, easily handled, solid electrophilic fluorinating agent. It is an equivalent of F_2, but much more effective and selective. In nucleoside chemistry, selectfluor is widely used to introduce a fluorine atom into heterocyclic bases *via* electrophilic substitution. Selectfluor can also selectively fluorinate certain sugar moieties, which possess electron-rich double bonds *via* an electrophilic addition.

iv. N-fluorobenzenesulfonimide-NFSI reagent

Although N-fluorosulfonamides are fairly weak fluorinating reagents, N-fluorosulfonimides, such as N-fluorobenzenesulfonimide (NFSI), are very effective and in common use.[18]

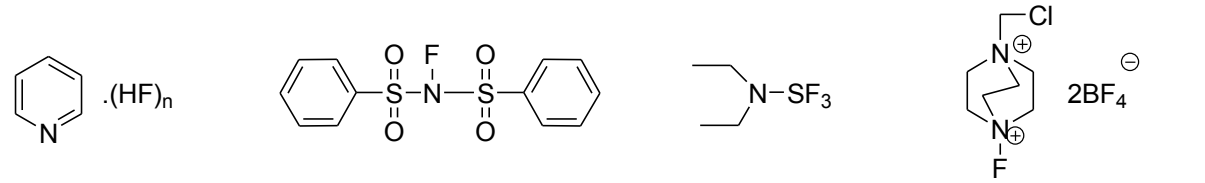


Figure 2

Conclusions

In this review, synthetic methods of certain fluorinated nucleosides have been covered. Introduction of fluorine atom, as a mimic of hydrogen or hydroxyl group into the sugar moiety of the nucleoside dramatically changes the physical-chemical properties of the nucleosides. The two main tactics that have been employed for the synthesis of fluorinated nucleosides are the installation of fluorine atom(s) into pre-modified precursor sugars before the introduction of nucleic bases and/or the regio- or stereo-selective introduction of fluorine atom(s) into suitably modified nucleoside derivatives. Among the above mentioned fluorinating agents, DAST seems to be the most commonly used for the fluorination of nucleosides. I hope that, with this mini review, I have provided an appropriate short description of the synthesis of fluorinated nucleosides and the most versatile fluorinating agents.

Acknowledgment

Author is thankful to Jubail Industrial College management for their support.

References

1. Ma T., Lin J.-S. Newton M.G., Chang Y.-C., Chu C.K. **1997**, *J. Med. Chem.*, **40**, 2750-2754.
2. Damha M.J., Wilds C.J., Novonha A., Brunker I., Brokow G., Arion D., Parniak M. A. **1998**, *J. Am. Chem. Soc.*, **120**, 12976-12977.
3. Elzagheid M.I., Viazovkina E., Damha M.J. **2002**, *Current protocols in Nucleic Acids Chemistry*, 1.7.1-1.7.19.
4. Wilds C.J., Damha M.J. **2000**, *Nucl. Acids Res*., **28**, 3625-3635
5. Pankiewicz K.W. **2000**, *Carbohydr. Res*., **327**, 87-105.
6. Kodama T., Matsuda A., Shuto S. **2006**, *Nucleic Acids symposium series*, **50**, 3-4.
7. Herdwjn P., Van Aerschot A., Kerremans L. **1989**, *Nucleosides, Nucleotides*, **8(1),** 65-96.
8. Takamatsa S., Katayama S., Hirose N., Delock E., Schelkens G., Demillequand M., Brepoels J., Izawa K. **2002**. *Nucleosides, Nucleotides, Nucleic Acids*, **21 (11, 12),** 849-861.
9. Watanabe K.A, Su T.-L, Klein R.S., Chu C.K., Matsuda A., Chun M.W., Lopez C., Fox J. **1983**, *J. Med. Chem.*, **26**, 152-156.
10. Elzagheid M.I., Viazovkina E., Damha M.J. **2002**, *Current Protocols in nucleic acids chemistry*, 1.7.1-1.7.19.
11. Elzagheid M.I., Viazovkina E., Damha M.J. **2003**, *Nucleosides, Nucleotides, Nucleic Acids*, **22**, 1339-1342.
12. Damha M.J., Wilds C.J., Novonha A., Brunker I., Brokow G., Arion D., Parniak M.A. **1998**, *J. Am. Chem. Soc.,* **120**, 12976-12977.
13. Wilds C.J., Damha M.J. **2000**, *Nucl. Acids Res*., **28**, 3625-3635.
14. Lok C.N., Viazovkina E., Min K.L., Nagy E., Wilds C.J., Damha M.J. Parniak M.A. **2002**, *Biochemistry*, **41**, 3457-3467.
15. Hansske F., Madej D., Robins M. J. **1984**, *Tetrahedron*, **40**, 125-135.
16. Olah G. A., Welch J. T., Yankar Y. D., Nojima M., Kerekes I., Olah J. A. **1979**, *J. Org. Chem*.,**44**, 3872-3881.
17. Middleton W. J., Bingham E. M. **1979**, Org. Synth., **57**, 50.
18. Liu P., Sharon A., Chu C.K. **2008**, *J. Fluor. Chem*., **129 (9)**, 743-766.