The Reaction of 2′-Deoxynucleosides with *N*-(2-Chloro-1,1,2-trifluoroethyl)diethylamine: Mechanisms of O^2,3′-Anhydro-2′-deoxynucleoside and By-product Formation

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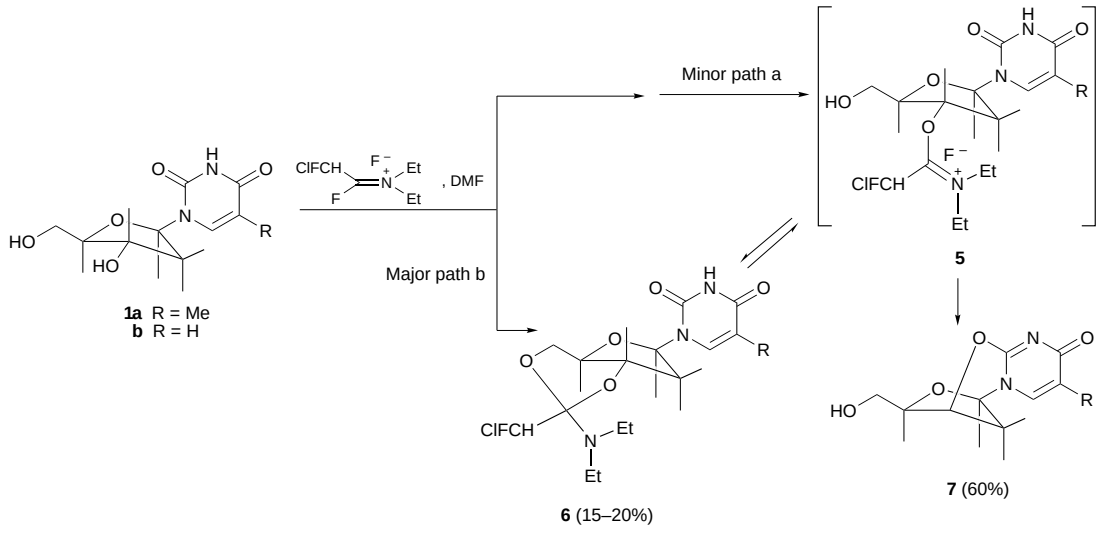
Reaction mechanisms consistent with the formation of isopropylidene-like *trans*-furanose-3′,5′-[2-(*R*)(*S*)-aminochloro-fluoromethyl-1,3-dioxanyl]-2′-deoxynucleoside intermediates **6**, O^2,3′-anhydro-2′-deoxynucleosides **7** and other minor reaction products and the yield-limiting effect of **6** on the cyclization of **7** are proposed.

In our ongoing efforts to develop anti-HIV liponucleotides with distinct biophysical properties, the synthesis of the immediate anhydro precursors (**7a**, **7b**) of azidothymidine and azidodeoxyuridine *via* reaction of 2′-deoxynucleoside series of compounds with *N*-(2-chloro-1,1,2-trifluoroethyl)-diethylamine (CTFDA) was investigated in detail.[5a,7,9]

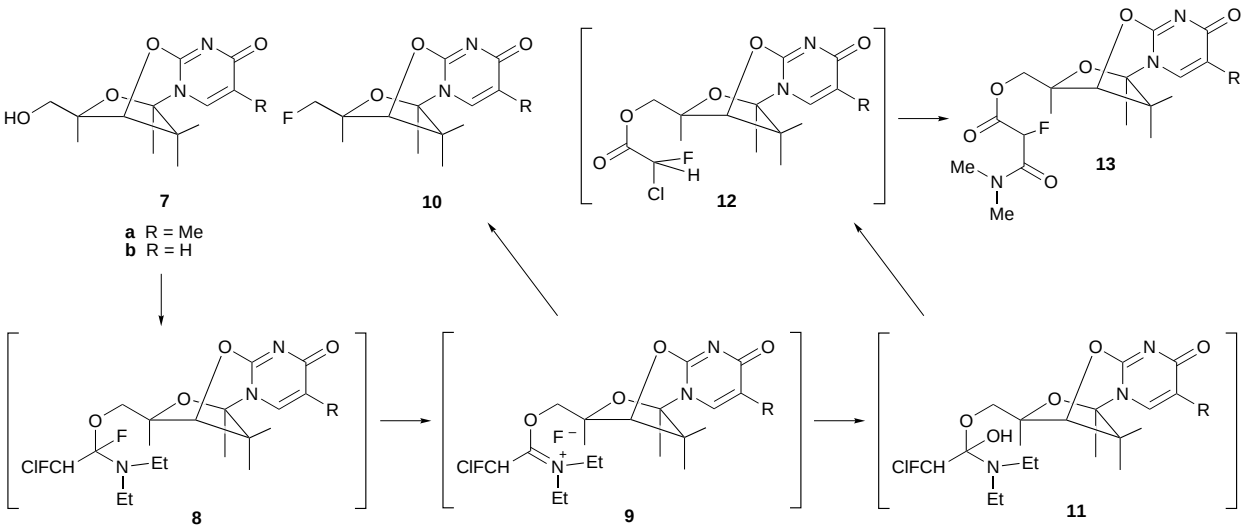
We herein report our preliminary findings on the reaction mechanism underlying the formation of O^2,3′-anhydronucleosides and by-product analysis envisaged to optimize the reaction conditions for this intriguing transformation.

The main features of the proposed mechanism as outlined in Schemes I and II are an equilibrium between the *trans*-furanose intermediates **6** and **5**, with the latter iminium species undergoing intramolecular cyclization to form anhydronucleosides **7**.

To rationalize the formation of the minor novel product

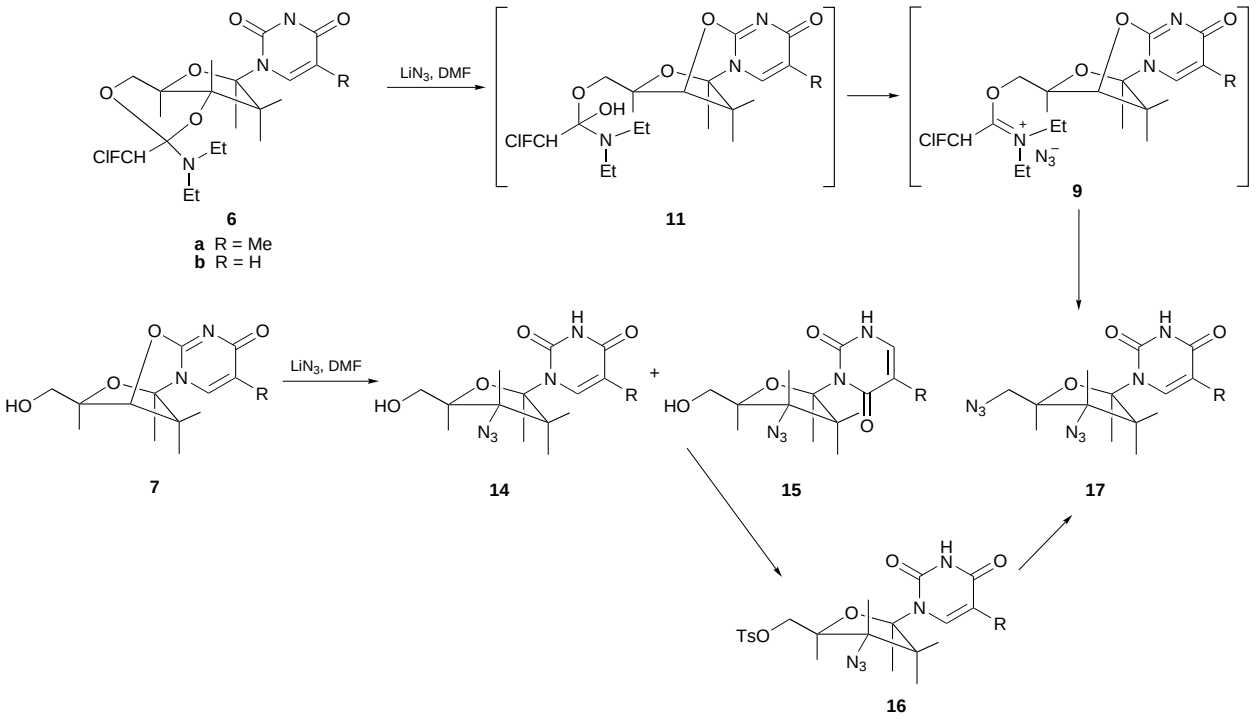


Scheme I



Scheme II

*To receive any correspondence.
†This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1998, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.



Scheme III

13a, analogous intermediates **8a**, **9a** and **12a** are invoked. The extremely acidic hydrogen atom of the chlorofluoromethyl group of **12a** is readily removed *via* base, with the resulting intermediate fluorocarbene inserting into the C—H bond of the solvent (DMF); elimination of hydrogen chloride to the enolate gives rise to the isolated ester **13a** (preferred keto form).

Azide displacements on the stable bicyclic intermediates **6** with lithium azide in DMF afforded the corresponding disubstituted derivatives **17** (Scheme III) *via* the likely intermediates **11** and **9**. The stereochemical course of the resulting diazido nucleosides having the 3′-α-stereochemistry was ascertained and confirmed by an independent synthetic route.

The products of reaction of 2′-deoxycytidine with CTFDA proved too unstable to isolate chromatographically (silica gel).

Techniques used: ^{1}H NMR, MS, IR

References: 18

Schemes: 4

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