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NUCLEOSIDE SYNTHESIS BY ALKYLATION WITH 2',3',5'-TRI-O-BENZOYL-D-RIBOFURANOSYL TRIFLATE

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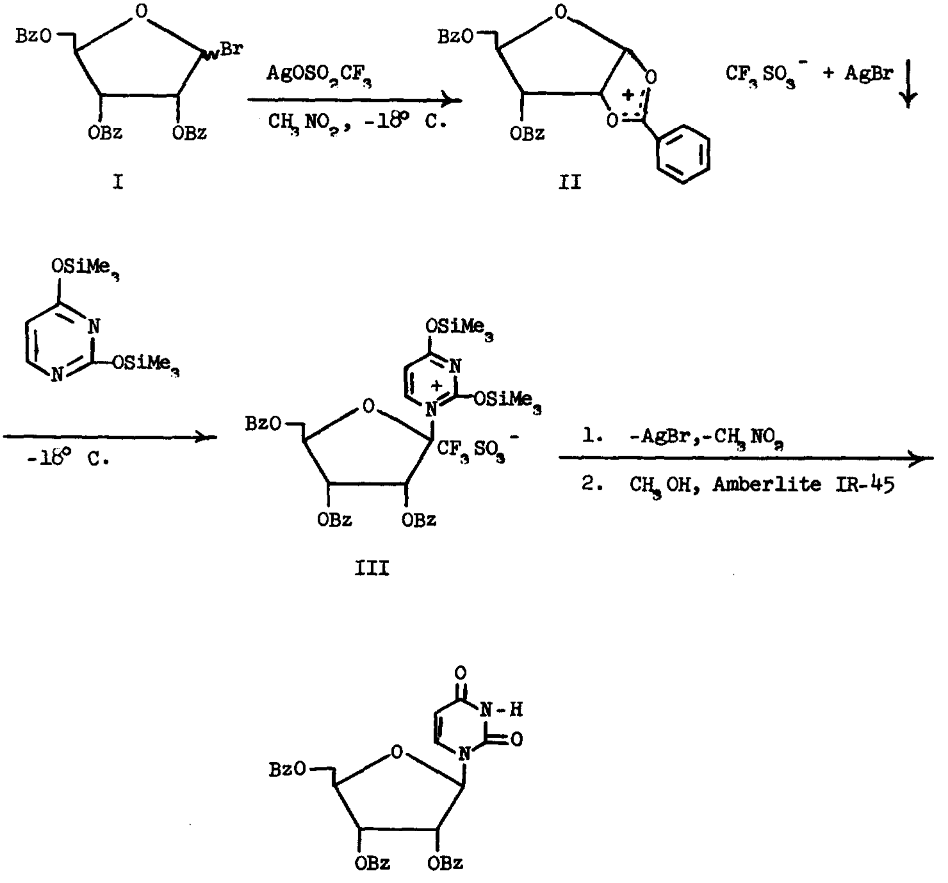
The use of derivatives of trifluoromethylsulfonic acid in synthesis has been explored by several investigators.[1,2] Trifluoromethylsulfonates ("triflates")[3] in particular have been utilized as exceptionally reactive alkylating agents.[4] The use of triflates in carbohydrate[5] and nucleoside[6] synthesis has also recently been noted. We wish to report the utility of 2',3',5'-tri-O-benzoyl-D-ribofuranosyl triflate, II, for nucleoside synthesis.



I

II

III

IV

The synthesis of uridine 2',3',5'-tri-O-benzoate, IV, is illustrative. When 2',3',5'-tri-O-benzoyl-D-ribofuranosyl bromide, I, (0.3M in nitromethane) is added to a 0.2M solution of silver triflate, 2',3',5'-tri-O-benzoyl-D-ribofuranosyl triflate, II, and silver bromide are formed. Addition of a 0.6M solution of 2,4-trimethylsilyoxypyrimidine to the slurry of II and silver bromide gives the pyrimidinium triflate III. Methanolysis of this intermediate provides nucleoside IV. The generality of the procedure is illustrated in Table I.

Table I

Silylated Heterocycle	Solvent	Addition[1] Temp., °C.	Nucleoside[2]	% Yield	% AgBr
uracil	CH_3NO_2	-18°	uridine 2',3',5'-tri-O-benzoate[3]	62	73
cytosine	CH_3NO_2	-18°	cytidine 2',3',5'-tri-O-benzoate[4]	50	68
5-methyl-2-pyridone	CH_3NO_2	0°	5-methyl-1-(2',3',5'-tri-O-benzoyl-β-D-ribofuranosyl)-2-pyridone	59	83
5-methyl-2-pyridone	CH_2Cl_2	-70°	5-methyl-1-(2',3',5'-tri-O-benzoyl-β-D-ribofuranosyl)-2-pyridone	75	99
4-methoxy-2-pyridone	CH_2Cl_2	-70°	4-O-methyl-3-deazauridine-2',3',5'-tri-O-benzoate	75	97

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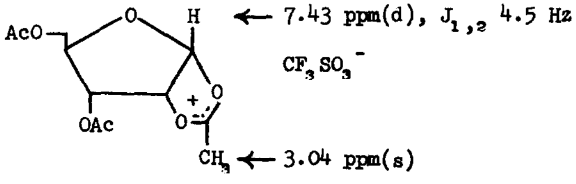
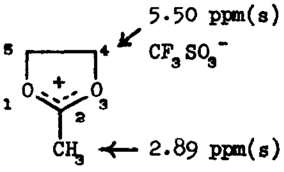
1. After addition of silylated heterocycle the reaction mixture was allowed to warm to ambient temperature overnight.
2. All nucleosides gave satisfactory elemental analyses.
3. m.p. 141-42°, lit. 142-43°.[15]
4. m.p. 175-76°, lit. 174.5-175.5°.[17]

Several noteworthy aspects of the synthesis are: (a) The best yields are obtained in methylene chloride at -70° C. Under these conditions it is likely that only low concentrations of the triflate II are achieved and that it is consumed as it is generated by reaction with the silylated heterocycle. (b) The intermediate pyridinium or pyrimidinium triflate may be partially converted to nucleoside prior to methanolysis. The results of Vorbrüggen[6] show that the 2-trimethylsilyoxy group of III is sufficiently reactive toward triflate anion to undergo slow displacement to furnish nucleoside and trimethylsilyl triflate. (c) In nitromethane at -18° C. II is generated in high concentration since good yields of silver bromide are obtained upon addition of bromide I.

(d) The alkylation produces only beta (trans) nucleosides. This is consistent with the bicyclic 2-phenyl-1,3-dioxolenium cation II acting as a stereospecific alkylating agent. The participation of 2'-acyloxy groups of halosugars in formation of 1,3-dioxolenium intermediate cations is common in ribonucleoside synthesis.[7] The directive effects of such participation frequently results in exclusive formation of beta isomers.[8] Indirect spectroscopic evidence for the existence of II as the predominant[9] alkylating agent in nitromethane is provided by pmr observations[10] of 2',3',5'-tri-O-acetyl-D-ribofuranosyl triflate, V.



V



VI

A prominent feature of the spectrum (-18° C.) of V is a low field methyl at 3.04 ppm. Similarly, 2-methyl-1,3-dioxolenium triflate, VI, exhibits a methyl resonance at 2.89 ppm while the haloacetate precursors of V and VI have methyl resonances at 2.07 ppm. Downfield shifts of the alpha hydrogens of 2-alkyl substituents is characteristic of 2-alkyl-1,3-dioxolenium cations.[11,12,13] Since Hart and Tomalia[12] have shown that little stability difference[14] exists between 2-phenyl and 2-methyl-1,3-dioxolenium tetrafluoroborate, the existence of cation II is supported.

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trimethylsilyl triflate as a catalyst in a facile nucleoside synthesis which probably proceeds thru 2',3',5'-tri-O-benzoyl-β-D-ribofuranosyl triflate as an intermediate.

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9. Integration of the low field (3.04 ppm) methyl of V versus the 3' and 5' methyls (2.10 and 2.20 ppm) indicates that cation V comprises 60% of the triacetates present. The identity of other specie(s) formed is being investigated.
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16. The author wishes to thank Dr. John Hill for helpful discussions and Ms. Ann Daiss for low temperature pmr spectra.
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