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CONTROL OF NUCLEOSIDE BASE STRUCTURE BY THE SELECTIVE REACTIVITY OF A RIBOSYLATED PYRIDINIUM TRIFLATE. A TOTAL SYNTHESIS OF 2-O-METHYL-3-DEAZAURIDINE

Robert L. Shone
Department of Chemical Research, Searle Laboratories,
P. O. Box 5110, Chicago, Illinois 60680

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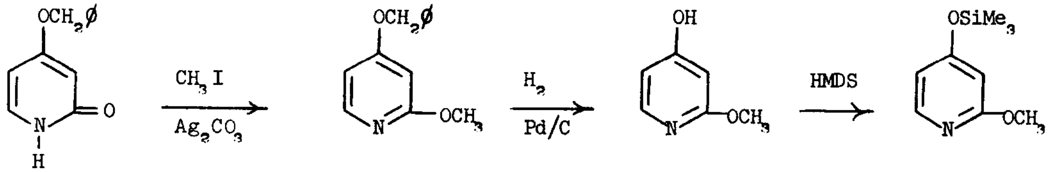
We wish to report a novel application of the 2',3',5'-tri-O-benzoyl-D-ribofuranosyl triflate alkylation synthesis of nucleosides[1,2] for the preparation of 2-O-methyl-3-deazauridine. The synthesis (Scheme II) employs a Hilbert-Johnson reaction[3] intermediate pyridinium triflate,[4] VII, that prefers to undergo silicon-oxygen bond cleavage (path b, Scheme II) rather than carbon-oxygen bond cleavage (path a, Scheme II). As a consequence only the desired 4-pyridone nucleoside, X, is produced. To our best knowledge this is the first example of the control of nucleoside base structure (paraquinoid vs. orthoquinoid) by effecting para substituent cleavage in a Hilbert-Johnson intermediate that also contains a reactive ortho function (methoxy).

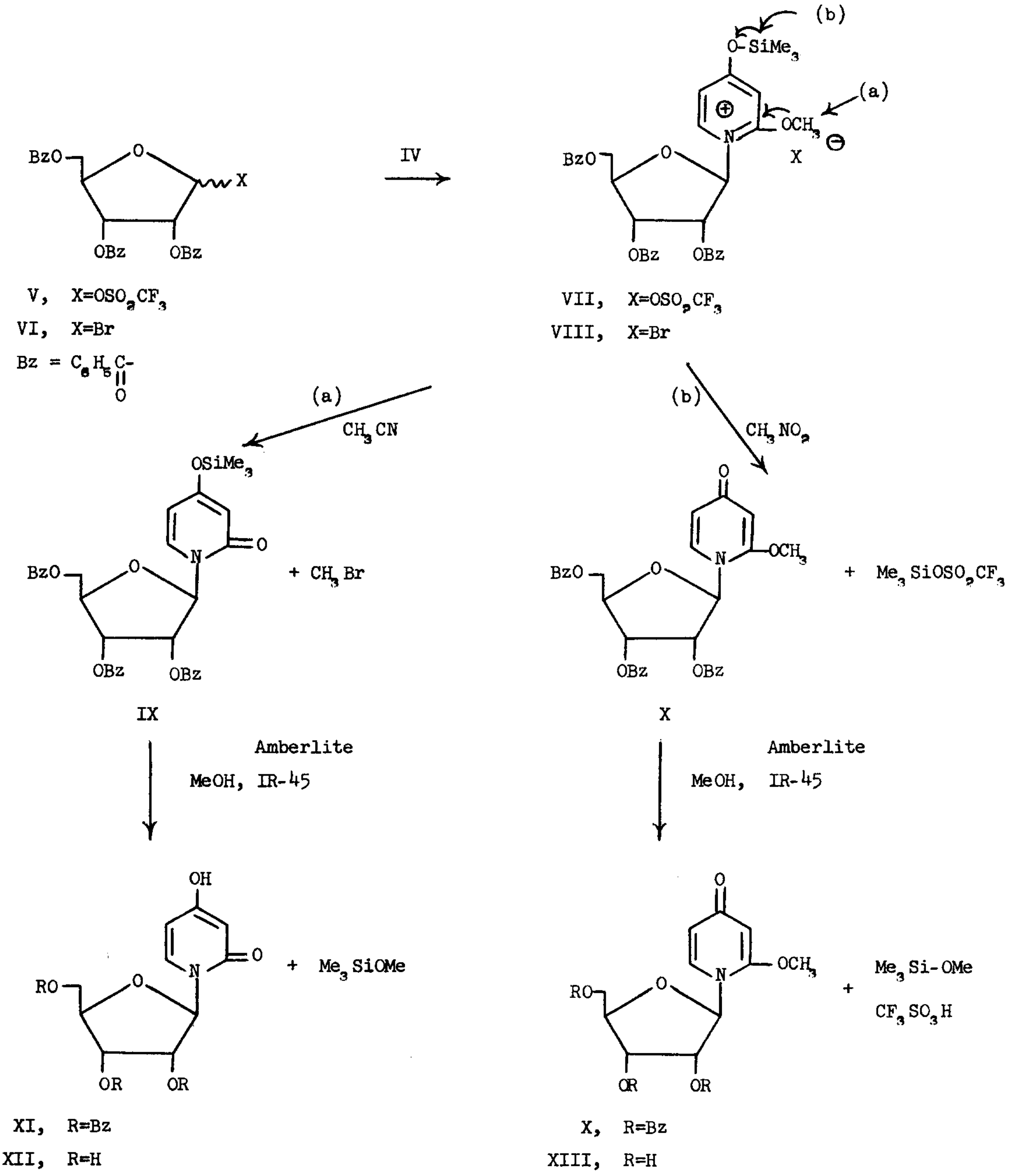
The preparative result of path a, Scheme I produces X as the sole nucleoside product[6] in good yield (51%). The synthesis begins with the preparation of 2-methoxy-4-trimethylsilyloxypyridine, IV, from 4-benzyloxy-2-pyridone,[7] I, as illustrated in Scheme I.



I   II, 71%   III, 85%   IV, 92%

Scheme I

The pyridone I is O-methylated to obtain II. The latter is then debenzylated by catalytic hydrogenation to 4-hydroxy-2-methoxypyridine,[8] III. Treatment of III with hexamethyldisilazane, distillation of IV (b.p. 48-50°/0.25 mm), and reaction with 2',3',5'-tri-O-benzoyl-D-ribofuranosyl triflate, V, (CH_3NO_2, -18° C.) produces the ribosylated pyridinium triflate VII.[9] Methanolysis of the resulting crude reaction mixture[1] followed by silica gel column chromatography furnished X (51%) as a pure glass;[10] λ_{max}^{MeOH} 254 nm (log ε, 4.32), $\alpha_D^{25°}$ -89.6°


V, X=OSO2CF3
VI, X=Br
Bz = C6H5C(=O)-
IV
(b)
O-SiMe3
(a)
OCH3
X ⊖
VII, X=OSO2CF3
VIII, X=Br
(a)
CH3CN
(b)
CH3NO2
OSiMe3
+ CH3Br
IX
OCH3
+ Me3SiOSO2CF3
X
Amberlite
MeOH, IR-45
Amberlite
MeOH, IR-45
OH
+ Me3SiOMe
XI, R=Bz
XII, R=H
OCH3
Me3Si-OMe
+
CF3SO3H
X, R=Bz
XIII, R=H
BzO
OBz
RO
OR

Scheme II

(c 1.0, CH_3OH), $\theta^{24°}_{254nm}$ -78,597, pmr ($CDCl_3$) δ 3.82 (3H, s, $-OCH_3$), 6.05 (1H, d of d, J=8.0 and 2.5 Hz, H_5), 6.23 (1H, "d", J_{app} 3.0 Hz, H_1'). $C_{32}H_{27}NO_9$ (569.54), calculated 67.48% C, 4.78% H, 2.46% N; found, 67.07% C, 4.80% H, 2.40% N. Debenzoylation of X with ammonia-methanol gave 2-O-methoxy-3-deazauridine, XIII (94%), m.p. 168-70°;[11] λ^{MeOH}_{max} 255 nm (log ϵ, 4.24), $\alpha^{25°}_{D}$ -25.2° (c 1.0, CH_3OH), pmr (DMSO-d_6) δ 3.85 (3H, s, $-OCH_3$), 5.65 (1H, d, J_{3-5} 2.5 Hz, H_3), 5.92 (1H, d of d, J=8.0 and 2.5 Hz, H_5), 5.80 (1H, d, J_{app} 4.5 Hz, H_1'), 5.92 (1H, d, J_{5-6} 8.0 Hz, H_6), $C_{11}H_{15}NO_6$ (257.24), calculated 51.36% C, 5.88% H, 5.45% N; found, 51.33% C, 6.00% H, 5.34% N.

The importance of the triflate anion for the success of Scheme II is emphasized by examination of the alkylation of IV with 2',3',5'-tri-O-benzoyl-D-ribofuranosyl bromide, VI (CH_3CN, room temperature). The more reactive pyridinium bromide VIII now undergoes Hilbert-Johnson cleavage (path a, Scheme II) at the ortho methoxy carbon-oxygen bond to produce XI (20% after purification) as the only observable nucleoside.[12] The contrasting reaction paths observed for pyridinium triflate VII and pyridinium bromide VIII is a reflection of the considerable difference in nucleophilicities of the two anions.

The following experimental procedure is typical for nucleoside syntheses using 2',3',5'-tri-O-benzoyl-D-ribofuranosyl triflate.[1] To a cooled (-18° C.) solution of silver triflate (2.57 g, 10 mmole) in dry nitromethane (60 ml.) is added dropwise with stirring solutions of (a.) 2',3',5'-tri-O-benzoyl-D-ribofuranosyl bromide[13] (5.44 g, 10 mmoles) in nitromethane (40 ml.) followed by (b.) 2-methoxy-4-trimethylsilyloxypyridine (1.80 g, 9.2 mmole) in nitromethane (30 ml.). After warming to room temperature and stirring overnight the reaction mixture is filtered (-AgBr), evaporated <u>in vacuo</u> ($-CH_3NO_2$), and quenched with methanol (300 ml.) and excess Amberlite IR-45(OH^-) by stirring two hours. Filtration, solvent evaporation, and elution chromatography gave 2',3',5'-tri-O-benzoyl-2-O-methyl-3-deazauridine (2.67 g, 51%).

References and Notes

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6. M. J. Robins and A. S. K. Lee, J. Med. Chem., 18, 1070 (1975), prepared XIII by preparative thin layer chromatography of a 2:1 mixture of 4-O-methyl and 2-O-methyl-3-deazauridine obtained by treatment of 3-deazauridine with diazomethane.

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9. The stability of VII under the present reaction conditions (CH_3NO_2, -18° C. and room temperature) has not been investigated.

10. Only nucleosides of beta configuration have been obtained using the 2',3',5'-tri-O-benzoyl-D-ribofuranosyl triflate alkylation method.

11. Literature m.p. 171-72°, see reference 6.

12. Pmr and tlc observation cannot exclude the presence of traces of X ($<$ 1%).

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14. Gratitude is expressed to A. Damascus, M. Scaros, B. Smith, and E. Zelinski as respective heads of the Spectroscopy, Hydrogenation, Separations, and Microanalytical departments of Searle Laboratories for services extended in support of this work.