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CONVERSION OF VINYLSILANES TO VINYL HALIDES WITH XENON DIFLUORIDE AND METAL HALIDES. A VERSATILE NEW ROUTE TO 5-(2-HALOVINYL)PYRIMIDINE NUCLEOSIDES[1]

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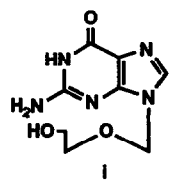
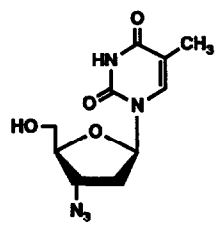
Summary: Addition of a protected 5-(2-trimethylsilylvinyl)uracil nucleoside to suspensions of xenon difluoride and alkali metal halides in benzene (or other solvents) resulted in rapid formation of the corresponding 5-(2-halovinyl)uracil products (*E*-isomer predominating).

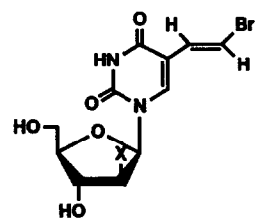
The presently optimistic outlook for chemotherapeutic intervention in viral-induced diseases resulted from the demonstration of highly selective and non-toxic treatment of herpes simplex infections with the guanosine nucleoside analogue, acyclovir[2] (**i**), and more recent success in the treatment of AIDS with AZT[3] (**ii**). This has produced a renaissance in the chemistry of nucleic acid related compounds and the successful discovery of a number of nucleoside and nucleotide analogues with potent antiviral activity.[4]



I



II



III X = H
IV X = OH

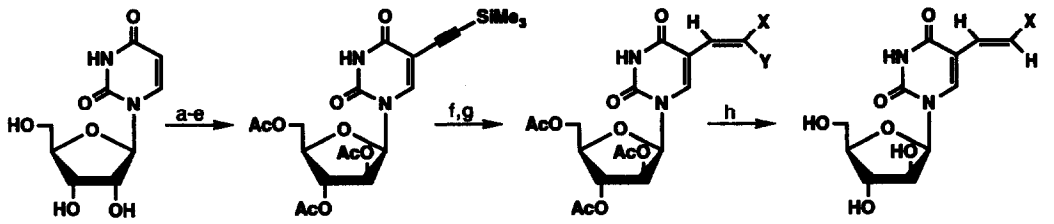
Jones, Walker, De Clercq and coworkers found 5(*E*)-(2-bromovinyl)-2'-deoxyuridine (BVDU, **iii**) to be a potent inhibitor of herpes simplex virus type 1 (HSV-1) that is selectively "activated" in viral-infected cells via 5'-phosphorylation by a viral-encoded thymidine kinase (TK).[5] Unfortunately, **iii** suffers enzymatic glycosyl bond phosphorolysis readily *in vivo*. Activation of its analogue, 1-(β-D-arabinofuranosyl)-5(*E*)-(2-bromovinyl)uracil (BVAraU, **iv**), by TK again results in potent and selective antiviral activity. The very limited phosphorolytic cleavage of **iv** makes BVAraU a promising antiherpes agent.[6]

An animal model study with a TK-activated ^{14}C-labeled nucleoside demonstrated successful non-invasive imaging of herpes infections,[7] but that isotope is not applicable in clinical medicine. Work in this area has been limited by rapid glycosyl cleavage with XVDU compounds and difficulties in synthesizing 2'-fluoronucleosides. Thus, we have targeted the promising radiohalogenated 1-(β-D-arabinofuranosyl)-5(*E*)-(2-halovinyl)uracils (*XVAraU) as candidates for non-invasive diagnosis of TK-positive herpes viral infections.

Conversion of 5-vinyluracil to 5-(2-halovinyl)uracils and coupling base derivatives with functionalized sugars to give α and β anomers of 5-(2-halovinyl)uracil deoxynucleosides[8] has been supplanted by organometallic couplings of acrylic acid esters with pyrimidine 2'-deoxy and arabinofuranosyl nucleosides followed by saponification and modified Hunsdiecker decarboxylative halogenations.[9] Radiohalogenations have employed halogen exchange, neutron activation, and modified Hunsdiecker methodologies.[10] However, harsh conditions, different precursors, specialized equipment, and moderate yields limit some approaches.

The ceric ammonium nitrate-mediated iodination, bromination, and chlorination of uracil bases and nucleosides has been reported.[11] We now describe a mild conversion of vinylsilanes to vinyl iodides, bromides, and chlorides with xenon difluoride and alkali metal halides. XeF_2 has been employed for electrophilic fluorination,[12] but this appears to be its first use as an oxidant for the mediation of electrophilic halogenation with metal halides. These solid reagents are convenient for the small quantities used in radiohalogenations.

Uridine (**1**) was converted in five stages to 1-(2,3,5-tri-*O*-acetyl-β-D-arabinofuranosyl)-5-[2-(trimethylsilyl)ethynyl]uracil (**2**, 58%).[13] Lindlar hydrogenation[14] of **2** gave 1-(2,3,5-tri-*O*-acetyl-β-D-arabinofuranosyl)-5(*Z*)-[2-(trimethylsilyl)vinyl]uracil [**3**(*Z*), 70%].[13] This *Z* vinylsilane appears to undergo a remarkable solvent-dependent isomerization upon standing in benzene solution at ambient temperature. Integration of the vinyl proton peaks[15] (and difference nOe enhancements of the vicinal vinyl proton and uracil H6 peaks, respectively, upon irradiation at the trimethylsilyl proton frequency) indicated an ~95:5 **3**(*E*/*Z*) mixture. Evaporation of this benzene solution followed by dissolution of the residue in ethanol resulted in rapid reversion to **3**(*Z*).[13] Both geometric isomers of **3** served as precursors for the 5-(2-halovinyl)uracil compounds (**4**-**6**),[16] but **3***E* was much less reactive. Isomer ratios of **4**-**6** varied with apparent solvent polarity in addition to the halide used. The *E*/*Z* ratios were highest with benzene followed by chloroform and methylene chloride and lowest with acetonitrile. Quantitative deacetylation was effected with NH_3/MeOH at ambient temperature to give the homogeneous (TLC, HPLC) 1-(β-D-arabinofuranosyl)-5(*E*)-(2-halovinyl)uracil (**7**) compounds.



1 2 3 *E*(*Z*): X(Y) = $SiMe_3$, Y(X) = H 7
4 *E*(*Z*): X(Y) = I, Y(X) = H
5 *E*(*Z*): X(Y) = Br, Y(X) = H
6 *E*(*Z*): X(Y) = Cl, Y(X) = H

(a) $(PhO)_2CO/NaHCO_3/DMF/\Delta$. (b) $NaOH/H_2O$. (c) $Ac_2O/DMAP$. (d) $ICl/CH_2Cl_2/\Delta$. (e) $HC{\equiv}CSiMe_3/(Ph_3P)_2PdCl_2/CuI/Et_3N/50$ °C. (f) H_2/Lindlar catalyst/quinoline/EtOAc. (g) XeF_2/M^+X^-/benzene. (h) NH_3/MeOH.

This six-stage conversion of uridine (**1**) to 1-(2,3,5-tri-*O*-acetyl-β-D-arabinofuranosyl)-5(*Z*)-[2-(trimethylsilyl)vinyl]uracil [**3**(*Z*), 41%][13] provides a substrate for the efficient synthesis of 1-(β-D-arabinofuranosyl)-5(*E*)-(2-halovinyl)uracils (**7**). Xenon difluoride is a convenient oxidant for the stoichiometric incorporation of chloride, bromide, or iodide from alkali metal halides (presumably via *in situ* generation of halonium fluorides) at the vinyl carbon of the precursor vinylsilane with predominantly *E* stereochemistry. This mild method for the synthesis of terminal vinyl halides provides a route for vinyl radiohalogenation not anticipated by methods noted in a very recent review.[18] An alternative oxidant, experimental and spectral details, and biological studies will be reported separately.[13]

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15. ^{1}H NMR (200 MHz, $CDCl_3$): **3***E*: δ 6.59 & 6.62 [d's (collapsed), $^2J_{vin}$ = 19.8 Hz, 1 & 1, vin H2(1) & H1(2)]; **3**(*Z*): δ 5.90 (d, $^2J_{vin}$ = 14.8 Hz, 1, vin H2), 6.92 (dd, $^4J_{vin\text{-}H6}$ = 1.2 Hz, 1, vin H1).
16. To a stirred suspension of XeF_2 (57 mg, 0.337 mmol) in anhydrous benzene (2 mL) under an argon atmosphere at ambient temperature was added solid LiCl, LiBr, or NaI (0.33 mmol). The mixture immediately turned pale yellow (LiCl), brown (LiBr), or ruby red (NaI). After a few minutes, **3**(*Z*) (154 mg, 0.33 mmol) was added. Essentially complete conversion of **3**(*Z*) to **4-6** within 15 min was indicated by HPLC [C_{18} reversed phase, H_2O/MeOH, 7:13; **4-6** had shorter retention times than **3**(*Z*)]. The mixture was diluted with CH_2Cl_2 (5 mL), washed quickly with 2% $NaHSO_3$/H_2O, and H_2O, and flash evaporated. The residue was purified by semi-preparative HPLC (C_{18} reversed phase, H_2O/MeOH, 2:3) to give >98% of 1-(2,3,5-tri-*O*-acetyl-β-D-arabinofuranosyl)-5-(2-iodovinyl)uracil (**4**, *E*/*Z* >49:1),[17a] 83% of 1-(2,3,5-tri-*O*-acetyl-β-D-arabinofuranosyl)-5-(2-bromovinyl)uracil (**5**, *E*/*Z* ~3:1),[17b] and 65% of 1-(2,3,5-tri-*O*-acetyl-β-D-arabinofuranosyl)-5-(2-chlorovinyl)uracil (**6**, *E*/*Z* ~1.7:1).[17c]
17. ^{1}H NMR (200 MHz, $CDCl_3$): (a) **4***E*: δ 7.04 & 7.44 (d's, $^2J_{vin}$ = 14.6 Hz, 1 & 1, vin H2 & H1); **4**(*Z*): δ 6.52 & 7.24 (d's, $^2J_{vin}$ = 9.0 Hz, 1 & 1, vin H2 & H1). (b) **5***E*: δ 6.70 & 7.43 (d's, $^2J_{vin}$ = 13.8 Hz, 1 & 1, vin H2 & H1); **5**(*Z*): δ 6.44 & 7.07 (d's, $^2J_{vin}$ = 8.30 Hz, 1 & 1, vin H2 & H1). (c) **6***E*: δ 6.45 & 7.35 (d's, $^2J_{vin}$ = 13.6 Hz, 1 & 1, vin H2 & H1). **6**(*Z*): δ 6.29 & 6.69 (d's, $^2J_{vin}$ = 8.4 Hz, 1 & 1, vin H2 & H1).
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