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NOVEL NUCLEOSIDE ANALOGUES VIA DIRECT ATTACK OF CARBON NUCLEOPHILES ON NUCLEOSIDES CONTAINING EPOXY-SUGARS

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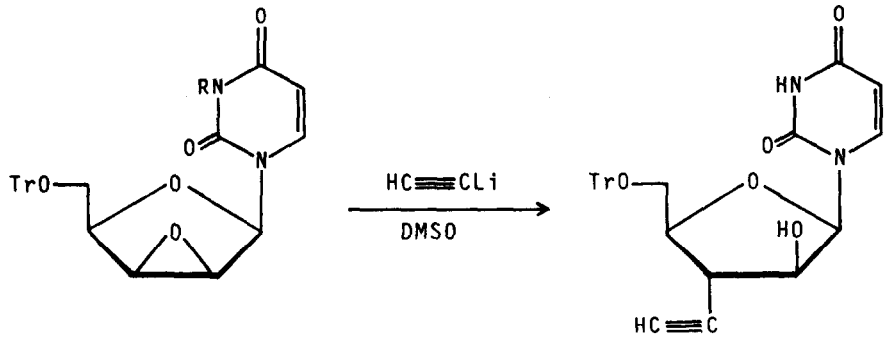
Abstract - Direct ring-opening of the epoxide ring in 1-(5'-O-trityl-2',3'-anhydro-β-D-lyxofuranosyl) uracil (1) by lithium acetylide or vinylmagnesium bromide/cuprous iodide affords the corresponding 5'-O-trityl-3'-C-substituted-3'-deoxy-ara-uridine species.

Nucleoside analogues are currently being widely investigated as potential antimetabolites,[1] and analogues of arabinonucleosides are of particular interest in view of the antitumour and antiviral activities of ara-cytidine and ara-adenosine.[2] Such analogues have frequently been generated by ring-opening of the oxirane ring of a lyxo-epoxide with a suitable nucleophilic species, such as a halide or pseudohalide, a procedure leading predominantly, if not exclusively, to formation of the 3'-substituted-3'-deoxy-ara-nucleoside.[3] However, this process does not seem to have been reported using carbon nucleophiles, and, indeed, such 3'-branched sugar nucleosides as have been described have generally been prepared via lengthy elaboration of the appropriately-branched sugars followed by condensation with nucleobases.[4] We report the utility of this approach in generating novel analogues of ara-nucleosides.

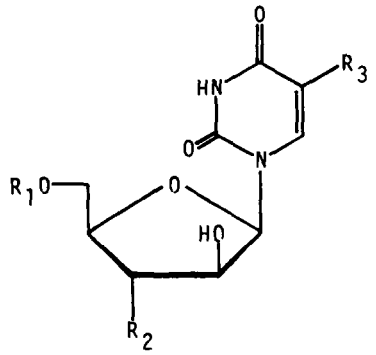
1-(5'-O-Trityl-2',3'-anhydro-β-D-lyxofuranosyl)uracil (1) is readily obtained in good yield in three steps from uridine.[5] Treatment of (1) with lithium acetylide and ethylenediamine in DMSO afforded 68% of 5'-O-trityl-3'-deoxy-3'-ethynyl-ara-uridine (2) together with 5% of a nucleoside by-product which has not been fully characterised. Detritylation of (2) using methanolic HCl afforded 3'-deoxy-3'-ethynyl-ara-uridine (3) (m.p. 199°C) in 94% yield.



(1) R = H

(9) R = Me

(2)



(3) R_1 = H; R_2 = C≡CH ; R_3 = H

(4) R_1 = H; R_2 = CH=CH_2; R_3 = H

(5) R_1 = H; R_2 = CH_2CH_3 ; R_3 = H

(6) R_1 = H; R_2 = CH_2CH_3 ; R_3 = CH_3

(7) R_1 = Tr; R_2 = CH=CH_2; R_3 = H

(8) R_1 = Tr; R_2 = Br ; R_3 = H

Reduction of (3) with Lindlar catalyst afforded (4) (m.p. 188°C) in ca. 90% yield. Further hydrogenation of (3) using 10% palladium-charcoal catalyst afforded 3'-deoxy-3'-ethyl-ara-uridine (5) (m.p. 183°C) in quantitative yield. Methylation of (5) using a Mannich reaction as described by Reese et al.[6] afforded 3'-deoxy-3'-ethyl-5-methyl-ara-uridine (6) (m.p. 184°C), a novel analogue of ara-thymidine, in 44% overall yield (based on (5)).

Since ring-opening of oxiranes by Grignard reagents in the presence of cuprous iodide as catalyst has been used with success in prostaglandin synthesis[7] and also in carbohydrates,[8] to give in general trans-diaxial products with inversion of configuration at the point of attack,[9] we investigated the use of these reagents with (1). Upon treatment with vinylmagnesium bromide (2.5 equivs.) and cuprous iodide (0.25 equivs.) in THF at -35°-0°C, 5'-O-trityl-3'-deoxy-3'-ethenyl-ara-uridine (7) was obtained in 10% yield and 5'-O-trityl-3'-bromo-3'-deoxy-ara-uridine (8) in 30% yield. No product resulting from ring-opening by attack at C-2' could be identified. Some 30% of (1) was also recovered. The major product thus arose via attack of the nucleophilic counterion of the Grignard reagent on the oxirane. Detritylation of (7) as above afforded 3'-deoxy-3'-ethenyl-ara-uridine (4) in 57% yield, identical in all respects to the material obtained using the previous route.

No ring-opening was observed if the corresponding N^3-methyl species (9)[10] was used in place of (1), and we speculate that co-ordination of a metal ion to the lactim tautomer at C-2 of the uracil ring may be required to facilitate this reaction.

The stereochemistry of the ring opening in (1) was shown by double-resonance ^{1}H n.m.r. studies performed on the sugar protons. The observed ^{1}H-^{1}H coupling constants (e.g. for (4), $J_{1'2'}$ = 6Hz, $J_{2'3'}$ = 8.5Hz, $J_{3'4'}$ = 10Hz)[11] are also consistent with those found in other 3'-substituted-3'-deoxy-ara-nucleosides.[12]

These results established the utility of carbon nucleophiles for opening the oxirane ring in nucleosides containing epoxy-sugars, here used to afford a novel rapid route to 3'-C-branched chain nucleosides and generate new ara-nucleoside analogues.[13]

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