Pergamon

Tetrahedron Letters 40 (1999) 4807–4810

TETRAHEDRON LETTERS

Synthesis of 2'-α-*C*-allenyl-2'-deoxyuridine : An Analogue of 2'-azido-2'-deoxyuridine, Known Inhibitor of Ribonucleotide Diphosphate Reductase (RDPR).

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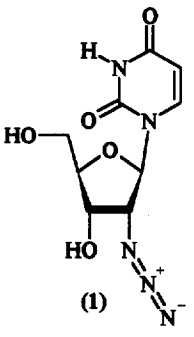
Received 18 March 1999; accepted 6 May 1999

Abstract : The 1,2-propadienyl (allenyl) group was introduced by means of a radical reaction at the 2'-α-C position of uridine to prepare the title compound as a novel analogue of 2'-azido-2'-deoxyuridine, a known inhibitor of RDPR.

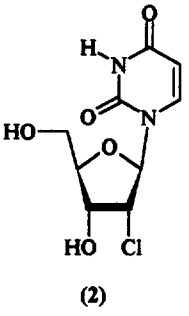
Keywords : nucleosides, radical reactions, rearrangement, allenes.

Ribonucleotide diphosphate reductase (RDPR) is the metalloenzyme that catalyzes the reduction of ribonucleotides to their 2'-deoxy counterparts.[1] The crucial importance of this enzyme in the development of tumors resulted in numerous studies directed towards the inhibition of RDPR.

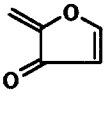
Among the modified nucleosides which were demonstrated to perform inhibition of RDPR as diphosphate derivatives, 2'-azido-2'-deoxyuridine (**1**) was shown to operate via a complex mechanism.[2] In the case of the extensively studied 2'-chloro-2'-deoxyuridine (**2**) the inhibition process implies abstraction of H-3' followed by loss of chloride ion and 1,2 hydrogen shift leading to the release of 2-methylene-3-(2H)-furanone (**3**).[3]



(1)



(2)



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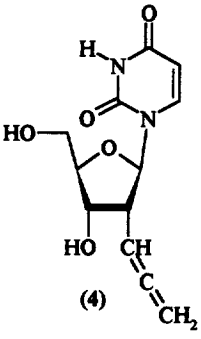

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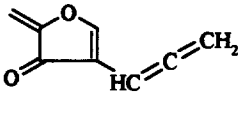


(5)

As regards to compound (**1**), if abstraction of H-3' is clearly established,[4] there is no loss of azide ion although the 2'-carbon nitrogen bond is cleaved prior or upon formation of a nitrogen centered radical and N_2.[3]

0040-4039/99/$ - see front matter
PII: S0040-4039(99)00917-X

As a part of a program aimed at the exploration of the properties induced by the presence of the 1,2-propadienyl (allenyl) residue in nucleoside chemistry,[5] we have decided to prepare 2'-α-C-allenyl-2'-deoxyuridine (**4**) as an analogue of the azido derivative (**1**). The allenyl group at C-2' is believed to induce a facile loss of the H-2' atom thus allowing further evolution leading to the formation of the sustituted 2-methylene-3-(2H)-furanone derivative (**5**).

The introduction of an unsaturated group at the C-2'-α position is scarcely documented : the graft of the allyl group was performed by radical reaction under photolytic conditions between allyltributyltin and either protected 2'-*O*-phenoxythiocarbonyluridine (yield 72-84 %)[6,7] or 2',5'-di-O-acetyl-2'-bromouridine.[7] Surprisingly the latter substrate was claimed to give rise to low yield (28 %) despite a long (5 days) reaction time in refluxing toluene.[7]

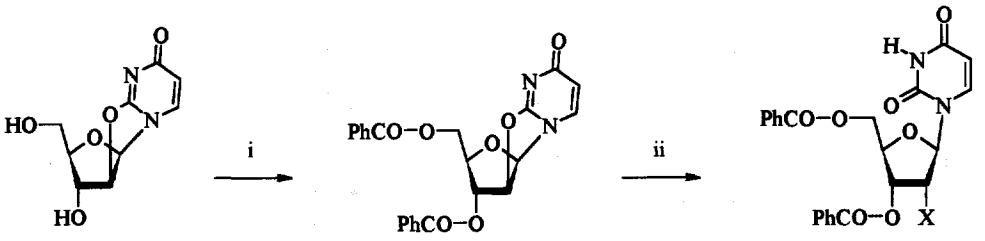
The work of Baldwin *et al.* has established that radical reaction between triphenylprop-2-ynyl stannane and alkyl bromides or iodides resulted in the formation of substituted allenes[8] (Scheme 1).

Scheme 1

$$Ph_3Sn\text{-}CH_2\text{-}C{\equiv}CH \;+\; R\text{-}Br \longrightarrow R{-}HC{=}C{=}CH_2 \;+\; Ph_3Sn\text{-}Br$$

During a previous study related to the 3'- position, we have established[5] that *O*-phenylthiocarbonate derivatives are unsatisfactory for this purpose in nucleoside chemistry : Therefore, despite the low yield quoted above, we turned ourselves towards the use of protected 2'-deoxy-2'-halogeno uridines. These compounds are easily obtained from the readily available 3',5'-di-*O*-benzoyl-2,2'-anhydrouridine[9] (**6**) by opening the anhydro ring with the suitable nucleophile thus affording the bromo- (**7a**)[10] or iodo- (**7b**)[11] derivative [Scheme 2].

Scheme 2

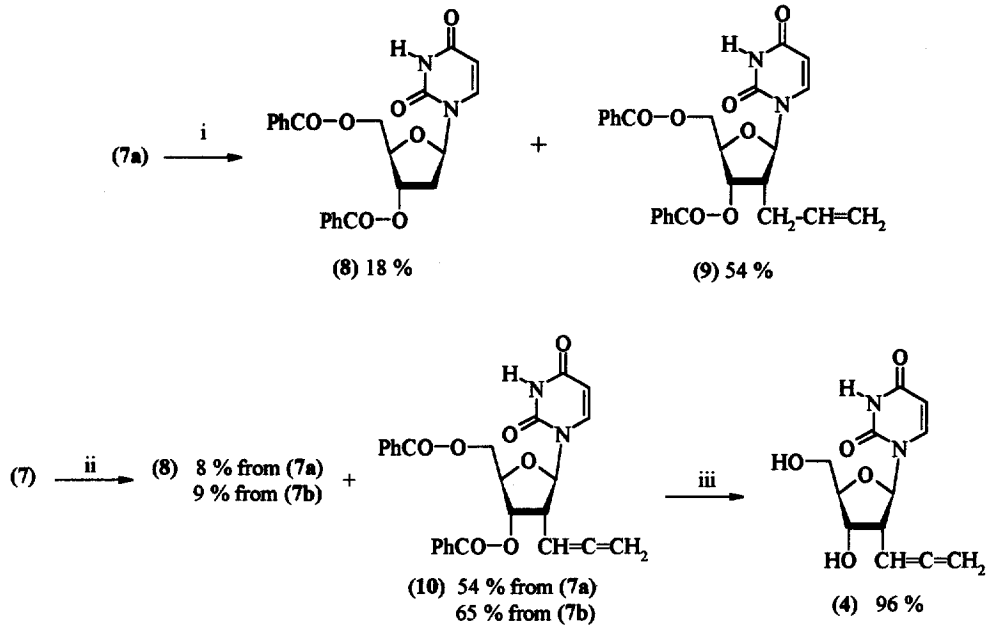


Reagents and conditions : i) Ph-CO-CN, Et_3N, MeCN; ii) LiBr or NaI, CF_3CO_2H, DMF, 85 °C;

First the reactivity of compound (**7a**) was tested under thermolytic conditions using AIBN as an initiator with allyltributyltin : the 2'-α-*C*-allyl derivative (**9**) was obtained in 54 % yield besides the 2'-deoxy compound (**8**) (18 %) [Scheme 3], thus demonstrating the feasability of the planned methodology. Although not reported by Grøtli and Undheim,[7] the formation of the "reduced" by-product was previously noticed by Chu *et al.* in a work related to thymidine series.[12]

The reaction between triphenylpropargyltin and the nucleoside derivatives (**7a,b**) was then examined in the same conditions as above. The expected transformation was observed [Scheme 3] and afforded - together with a low amount of the 2'-deoxy by-product (**8**) - the 2'-α-*C*-allenyl-2',3'-di-*O*-benzoyluridine (**10**). The reaction was better conducted on the iodo- substrate (**7b**) [65 % yield] than on the bromo- analog (**7a**) [54 %].

Scheme 3



Reagents and conditions : i) nBu$_3$Sn-CH$_2$-CH=CH$_2$, AIBN, benzene, reflux, 2 h. ; ii) Ph$_3$Sn-CH$_2$-C≡CH (5 equiv.), AIBN, benzene [7.5 mL/1 mmol of (7)], reflux, 5 h. ; iii) NaOMe (0.1 equiv.), MeOH, r t.

The deprotection of the 3'- and 5'- hydroxyl groups was performed as usual and afforded the free 2'-α-*C*-allenyl-2'-deoxyuridine (**4**)[13] in high yield.

The ^{1}H-NMR spectrum of (**4**) exhibited a signal at 5.99 ppm for H-1' (d, $J_{1',2'}$ = 9.0 Hz), in agreement with the corresponding published data for 2'-α-*C*-allyl compounds.[6,7] According to the work of Altona,[14] this

value of the $J_{1',2}$ coupling constant is consistent with a large preference (about 90 %) for the C-2' endo (S type) furanose conformer. By comparison with uridine ($J_{1',2'}$ = 4.8 Hz, 48 % S[14]) and particularly 2'-azido-2'-deoxyuridine ($J_{1',2'}$ = 5.1 Hz,[15] about 50 % S) this marked change of conformation would probably result in interesting properties for compound (**4**).

References and notes :

1. Stubbe, J.A. *Annu. Rev. Biochem.* **1989**, *58*, 257-285.
2. Salowe, S.; Bollinger, J.M.Jr; Ator, M.; Stubbe, J.; McCracken, J.; Peisach, J.; Samano, M.C.; Robins, M.J. *Biochemistry* **1993**, *32*, 12749-12760.
3. a) Harris, G.; Ator, M.; Stubbe, J. *Biochemistry* **1984**, *23*, 5214-5225. b) Ator, M.A. ; Stubbe, J. *Biochemistry* **1985**, *24*, 7214-7221.
4. Salowe, S.P.; Ator, M.A.; Stubbe, J. *Biochemistry* **1987**, *26*, 3408-3416.
5. Becouarn, S.; Czernecki, S.; Valéry, J.M. *Tetrahedron Lett.* **1995**, *36*, 873-876.
6. De Mesmaeker, A. ; Lebreton, J. ; Hoffmann, P. ; Freier, S.M. *Synlett* **1993**, 677-679.
7. Grøtli, M. ; Undheim, K. *Acta Chemica Scand.* **1995**, *49*, 217-224.
8. Baldwin, J.E.; Adlington, R.M.; Basak, A. *J. Chem. Soc. Chem. Commun.* **1984**, 1284-1285.
9. Holy, A. *Coll. Czech. Chem. Commun.* **1972**, *37*, 4072-4087.
10. a) David, S.; Auge C. *Carbohydrate Res.* **1973**, *28*, 125-128. b) Holy, A. *Coll. Czech. Chem. Commun.* **1976**, *41*, 3335-3340.
11. Holy, A. *Tetrahedron Lett.* **1971**, 185-187.
12. Chu, C.K.; Doboszewski, B.; Schmidt, W.; Ullas, G.W. *J. Org. Chem.* **1989**, *54*, 2767-2769.
13. Representative NMR data for compound (**4**) : ^{1}H-NMR (250 MHz, DMSO-d6) δ = 11.32 (broad s, NH), 7.85 (d, $J_{5,6}$ = 8.2 Hz, H-6), 5.58 (d, $J_{5,6}$ = 8.2 Hz, H-5), 5.99 (d, $J_{1',2'}$ = 9.0 Hz, H-1'), 5.60 (d, J = 4.7 Hz, 3'-OH), 5.20 (m, =CH), 5.10 (broad s, 5'-OH), 4.77 (m, $=CH_2$), 4.17 (m, H-3'), 3.88 (m, H-4'), 3.57 (m, H-5', H-5"), 2.90 (m, H-2'). ^{13}C-NMR (63 MHz, DMSO-d6) δ = 209 (=C=), 163, 151 (C-4 and C-2), 141 (C-6), 103 (C-5), 87.8 (C-1'), 87.2 (=CH), 84.4 (C-4'), 76.5 ($=CH_2$), 73.6 (C-3'), 62.5 (C-5'), 48.4 (C-2').
14. Altona, C.; Sundaralingam, M. *J. Am. Chem. Soc.* **1973**, *95*, 2333-2344.
15. Kirschenheuter, G.P.; Zhai, Y.; Pieken, W.A. *Tetrahedron Lett.* **1994**, *46*, 8517-8520.