Pergamon

Tetrahedron Letters, Vol. 36, No. 6, pp. 873-876, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(94)02383-2

Radical Mediated Synthesis of 3'-α-*C*-allenyl-2',3'-dideoxythymidine as a non-polar analogue of AZT.

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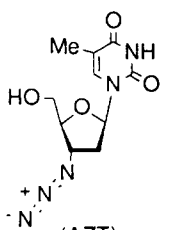
Abstract: *The 1,2-propadienyl (allenyl) group was selectively introduced at the 3'-α-C position by free radical C-C bond formation reaction involving triphenylprop-2-ynylstannane and protected 2',3'-dideoxy-3'-halogenothymidine.*

Since 3'-azido-2',3'-dideoxythymidine (AZT) was discovered as a selective anti-HIV agent[1] and introduced in wide clinical use,[2] a number of 2',3'-dideoxynucleoside analogues were targeted at the reverse transcriptase step.[3]

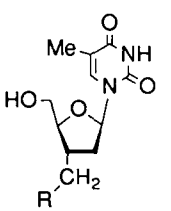
As a part of structure-activity relationships studies directed towards the precise role of the 3'-azido group, some 3'- carbon substituted 2',3'-dideoxynucleosides were prepared as non-polar analogues of AZT.[4-6]

Among them 3'-cyanomethyl-2',3'-dideoxythymidine (**A**) and 2',3'-dideoxy-3'-(2-propynyl)thymidine (**B**) were designed because of the claimed isosteric relationship of their carbon side chain with an azido group.[5]

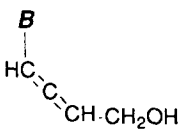
We thought that the 1,2-propadienyl (allenyl) moiety would better fit this criterion. Interestingly the allenyl residue (see Chart) is present in the structure of Adenallene and Cytallene which are acyclic nucleoside analogues exhibiting anti-HIV properties.[7] So we decided to prepare the 3'-α-*C*-allenyl-2',3'-dideoxythymidine (**1**) as a novel non-polar analogue of AZT.



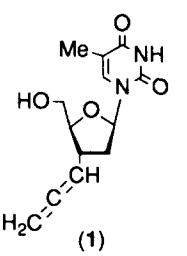
(AZT)



A, R = N≡C
B, R = HC≡C



B = adenosine , cytosine



(**1**)

Rather than using ionic reactions for our purpose we turned our attention to free radical methodology. It was shown that reaction between triphenylprop-2-ynyl stannane **2**[8] and alkyl

bromides, or preferably iodides, in the presence of radical initiator (AIBN) resulted in the formation of substituted alleneś[9] (Scheme 1).

Scheme 1

$$R^{\cdot} + \underset{\mathbf{2}}{HC{\equiv}C{-}CH_2\text{-}SnPh_3} \longrightarrow R{\cdot}CH{=}C{=}CH_2 + {\cdot}SnPh_3$$

$$RX + {\cdot}SnPh_3 \longrightarrow R^{\cdot} + XSnPh_3$$

X = Br, I

Moreover, free radical methodology was recently used to introduce the allyl side-chain at the 3'-α position starting from 5'-*O*-(*tert.*butyldimethylsilyl)-2'-deoxy-3'-*O*-(phenoxythiocarbonyl)thymidine.[4] But when this compound was reacted with the stannane **2** in toluene in the presence of AIBN only extensive degradation was observed. Thus in similarity with the original work by Baldwin[9] we had to perform the free radical reaction between **2** and a suitably iodinated nucleoside species.

We considered that such compounds could be favorably obtained from the protected 2,3'-anhydro derivative **3** which is easily prepared in high yield from thymidine by a tandem Mitsunobu reaction.[10] Rather than considering the action of the excessively acidic hydrogen iodide, we looked at a mild electrophilic reagent. Actually opening of the anhydro-ring was achieved by reaction between **3** and anhydrous magnesium iodide[11] in toluene at 110°C and cleanly afforded the *erythro* derivative **4** in 75% yield.

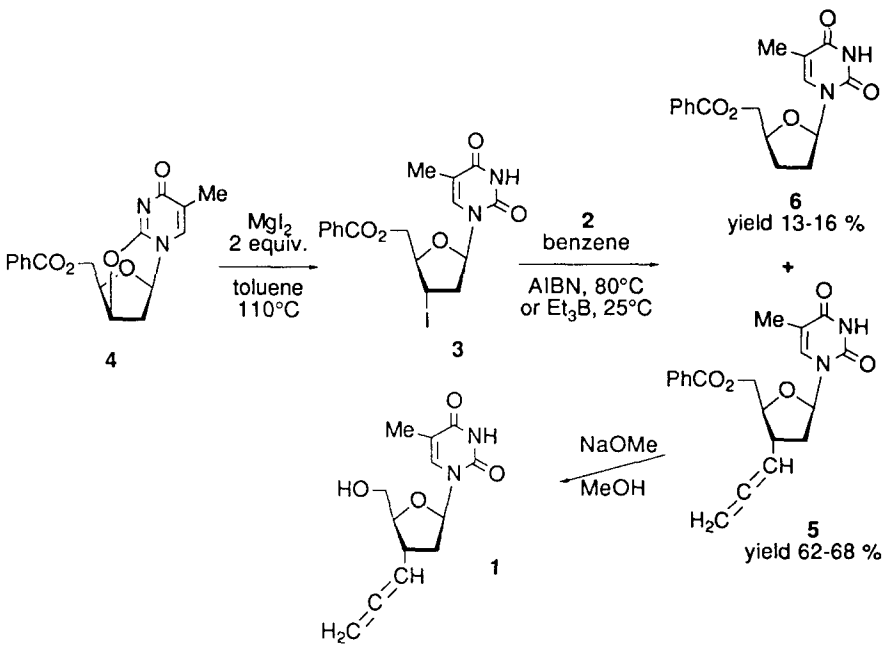
Further free radical reaction between compound **4** and the stannane **2** was performed under different conditions (see Scheme 2). Two compounds were obtained in similar proportions.

As previously noticed in the free radical allylation procedure,[4] the 2',3'-dideoxy derivative **6** was isolated as a minor by-product. Although the origin of this reduced product remains unclear we have checked that the mode of initiation has negligible effect on the amount of compound **6**.

The major product (62 to 68% yield according to conditions) was identified as 3'-α-*C*-allenyl-5'-*O*-benzoyl-2',3'-dideoxythymidine **5**[12]. The configuration at C-3' was established by X-ray spectroscopy (see Fig. 1).[13]

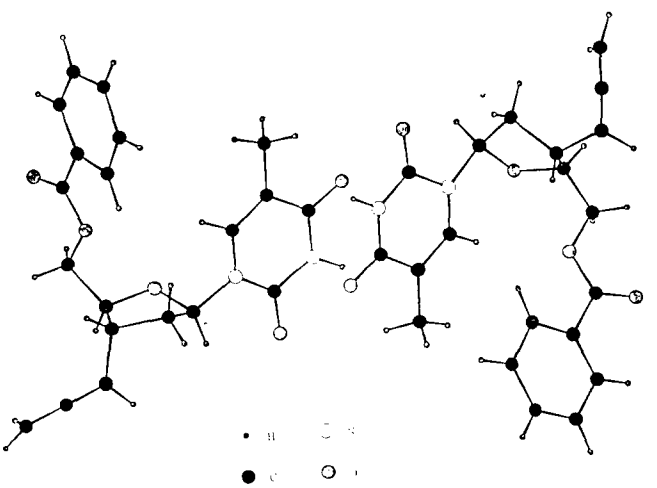
We have noticed that the use of triethylborane as an initiator[14] was much more efficient than the thermal initiation with AIBN: the reaction could be conducted at room temperature. This resulted in an important decrease of the thermal isomerization of the stannane **2** which is known to yield the more stable, and so less reactive, triphenyl-1,2-propadienylstannane $H_2C{=}C{=}CH\text{-}SnPh_3$.[15] By this way we were able to reduce the excess of reagent **2** to 4 equivalents - compare to 6 equiv. if AIBN was used - with maintained yield and more convenient work-up.

Scheme 2



Usual debenzoylation of **5** afforded the target compound **1**[12] which is currently screened against HIV.

Fig. 1: ORTEP of compound **5**



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12. All new compounds exhibited satisfactory spectral and analytical data.
13. Dr Y. Dromsee (Laboratoire de Chimie des Métaux de Transition, Université Pierre et Marie Curie) is acknowledged for performing the X ray cristallographic study on compound **5**.
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(*Received in France* 9 *November* 1994; *accepted* 7 *December* 1994)