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An Unusually Facile [3,3]-Sigmatropic Rearrangement in a Stereospecific Synthesis of Novel 2',3'-Dideoxynucleoside Precursors

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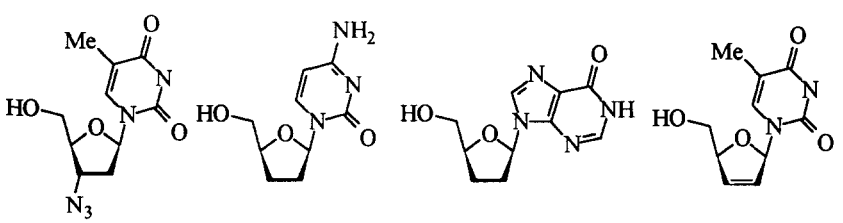
Abstract: *The glycal **5** is converted to intermediates which undergo, under mild conditions, thermal aza-Claisen rearrangements, leading to the amides **7** and **8** and the 2-pyrimidone **9**, all potential precursors to 2',3'-dideoxynucleosides.*

The intense interest in nucleoside chemistry which has emerged recently is a result of the use of a range of nucleosides and their analogues as therapeutic agents. Of particular relevance have been the 2',3'-dideoxy analogues, where compounds such as AZT **1**, ddC **2**, ddI **3** and d4T **4** represent important examples of compounds with activity against AIDS.

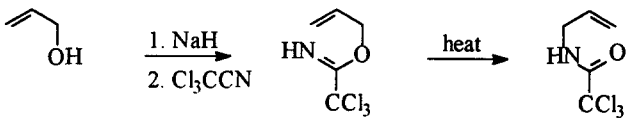


1 **2** **3** **4**

A number of synthetic approaches have been developed towards these dideoxy compounds, either from nucleosides or by total synthesis from simpler precursors.[1] The latter approach, usually involving a coupling between a functionalised sugar fragment and a suitable heterocyclic base, offers the advantage of more flexibility in structural variation of the two fragments. However the direct coupling often results in the production of both anomers, thus necessitating a separation procedure, although a number of methods have recently been developed to encourage β-anomer formation.[2]

We describe here a method, based on a particularly facile aza-Claisen rearrangement, which allows the preparation of stereochemically pure di- and tetrahydrofurans with promise as useful intermediates towards dideoxynucleoside analogues.

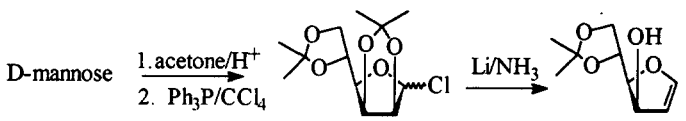
The [3,3]-sigmatropic rearrangement of imidates to amides was first developed into a useful synthetic method by Overman who showed that allylic alcohols react with trichloroacetonitrile to give the corresponding trichloroacetimidates, which undergo thermal rearrangement in refluxing xylene to afford trichloroacetamides (scheme 1).[3]



scheme 1

In some cases the rearrangement takes place at lower temperatures in the presence of catalytic amounts of mercury (II) or palladium (II) salts.[3,4] Similar chemistry has been developed more recently using trifluoroacetonitrile.[5] As usual with such concerted reactions the stereochemical control is excellent and highly predictable.

It was apparent to us that such a process carried out on a suitably hydroxylated 2,3-dihydrofuran could provide useful intermediates for nucleosides and we chose as our starting material the glycal **5**, which is readily available from D-mannose (scheme 2).[6] This glycal has been used previously as a substrate in the Ireland-modified Claisen rearrangement where it should be noted it behaved as a "normal" allylic alcohol, showing no apparent enhanced reactivity. [6]

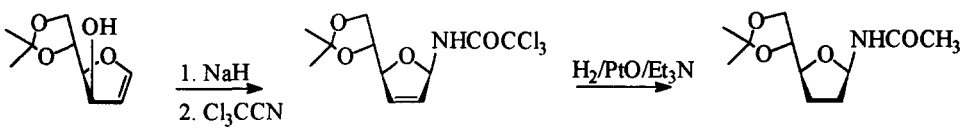


5

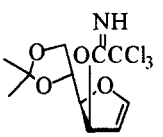
scheme 2

However, when we subjected **5** to the Overman conditions for the imidate-amide rearrangement (NaH, Cl_3CCN, ether, 0°) we were unable to observe the expected imidate **6** but instead isolated the rearrangement product **7** as a crystalline solid (78%).[7] This particularly facile aza-Claisen reaction seems to result from some subtle effect on the energy requirements for the rearrangement [8] caused by the oxygen atom on the double bond since in the corresponding carbocyclic system no such enhancement is observed.[9]

Reduction of **7** (H_2/PtO, EtOAc, Et_3N) produced the acetamide **8** as an oil (89%), the triethylamine being necessary to prevent extensive decomposition caused by the HCl produced in the hydrogenolysis.



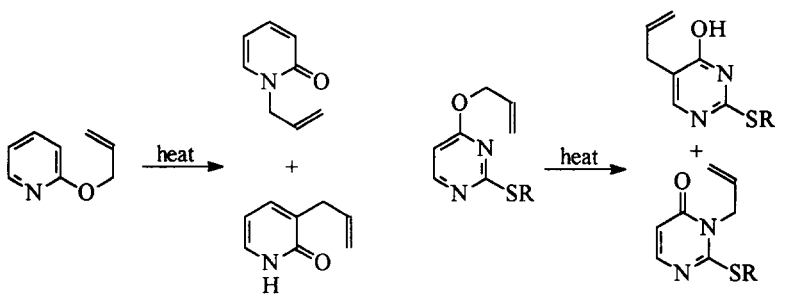
5 **7** **8**



6

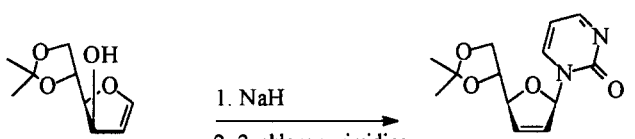
The facile synthesis of the amides **7** and **8** illustrates a method which could provide useful precursors towards analogues of 2',3'-didehydro-2',3'-dideoxy- and 2',3'-dideoxynucleosides respectively, since they have a suitably placed nitrogen atom for building on the requisite heterocyclic substituent. However we were attracted by the idea of modifying the chemistry described above in such a way as to directly deliver a heterocyclic

moiety attached to the sugar-derived fragment, and have therefore investigated the [3,3]-sigmatropic rearrangement of some 2-allyloxy pyrimidines. This particular type of reaction seems not to have been reported although closely related studies of 2-allyloxypyridines [10] and 2-substituted-4-allyloxypyrimidines [11] have appeared. In general the thermal Claisen rearrangements of these compounds was carried out in high boiling solvents at temperatures over 200°C and the product mixture contained approximately equal amounts of the respective C-alkyl and N-alkyl compounds (scheme 3). (With the corresponding 2-allyloxypyrimidine only the N-alkyl product could be formed by Claisen rearrangement). Later work showed that Lewis acid catalysis of the rearrangement of 2-allyloxypyridine allows a lower temperature to be used and that essentially only N-allyl-2-pyridone is formed,[12] while similar observations have been made for pyrimidine systems with palladium (II) catalysis.[13]



scheme 3

In model studies, we prepared 2-allyloxypyrimidine from 2-chloropyrimidine and allyl alcohol (NaH, THF, overnight reflux). This allyl ether showed no sign of rearrangement either in refluxing N,N-dimethylaniline (195°C) or on heating neat at 250°C. However when the glycal **5** was treated with sodium hydride followed by 2-chloropyrimidine (THF, reflux, 2 days), a much more polar product was formed. This was isolated by flash chromatography (ethyl acetate/methanol/triethylamine, 95:5:1) to give directly the Claisen rearranged N-alkyl-2-pyrimidone **9** in 61%yield.[14] There was no indication of the any other isomer in the reaction mixture.



5 **9**

This method offers a new, direct and stereospecific approach to 2',3'-dideoxynucleosides, and we are actively pursuing its development to compounds such as **2** and **4**.

Acknowledgements.
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14. Selected physical data. 7: m.p. 44-45°C; ν_{max} (KBr)/cm^{-1} 3380, 3320, 1720; δ_H(250 MHz; $CDCl_3$; *J*/Hz) 1.33(3 H, s), 1.42(3 H, s), 3.81(1 H, dd, *J*9, 5), 4.14(1 H, dd, *J*9, 7), 4.35(1 H, m), 4.78(1 H, m), 6.03(1 H, dt, *J*6, 1.5), 6.15(1 H, dt, *J*6, 1.5), 6.45(1 H, ddd, *J*9, 1.5, 1.5), and 7.69(1 H, br s, NH); δ_C(62.9 MHz; $CDCl_3$) 25.3, 26.3, 65.6, 76.4, 86.9, 87.5, 93.0, 110.5, 128.8, 130.1 and 161.0; m/z (FAB) 330/332 (MH^+), 169 (MH^+–$NHCOCl_3$). 9: oil; δ_H(250 MHz; $CDCl_3$; *J*/Hz) 1.29(3 H, s,), 1.33(3 H, s,), 3.85(1 H, dd, *J*9, 4.5), 4.12(1 H, dd, *J*9, 7), 4.29(1 H, dt, *J*7, 4.5), 4.84(1 H, m), 6.07(1 H, dt, *J*6, 1.5), 6.26(1 H, dt, *J*6, 1.5), 6.31(1 H, dd, *J*6.5, 4), 6.93(1 H, br t, *J*1.5), 8.22(1 H, dd, *J6.5, 3),*and 8.52(1 H, dd, *J*4, 3); δ_C(62.9 MHz; $CDCl_3$) 25.1, 26.5, 66.3, 76.6, 88.9, 92.9, 104.4, 110.7, 128.1, 132.3, 144.5, 156.1, 166.5; m/z (EI) 264(M+), 169, 164, 153, 138, 101, 43.

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