Regioselective Synthesis of 6*H*-Pyrano[3,2-*d*]pyrimidine-2,4(1*H*)-diones and Furo[3,2-*d*]pyrimidine-2,4(1*H*)-diones

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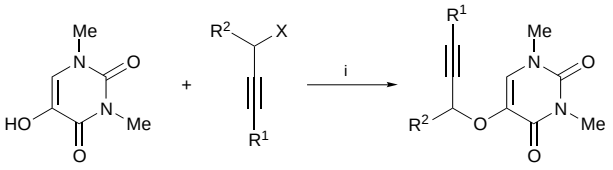
A number of 1,3-dimethyl-6*H*-pyrano[3,2-*d*]pyrimidine-2,4(1*H*)-diones (**4a–d**) and 1,3-dimethylfuro[3,2-*d*]pyrimidine-2,4(1*H*)-diones (**5a–c**) have been regioselectively synthesised in 88–94% and 80–90% yields respectively from the thermal [3s,3s] sigmatropic rearrangement of 1,3-dimethyl-5-(prop-2-ynyloxy)uracils (**3a–d**).

We have recently reported[1] the regioselective synthesis of pyrano[2,3-*c*]coumarins from aryloxybut-2-ynyloxy coumarins. There we established that it is possible to cyclise regioselectively the intermediate allenyl enol from the [3s,3s] sigmatropic rearrangement of the propynyl ethers of 3-hydroxycoumarin exclusively either to furo[2,3-*c*]coumarin or pyrano[2,3-*c*]coumarin simply by manipulating the reaction conditions. Literature reports[2] revealed that Otter *et al.* studied the Claisen rearrangement of 5-(prop-2-ynyloxy)-uracil under a variety of conditions. Although they succeeded in obtaining a mixture of varying proportions of furo[3,2-*d*]-pyrimidine-2,4-dione and 6*H*-pyrano[3,2-*d*]pyrimidine-2,4-dione they failed to isolate exclusively either of the products. This prompted us to undertake a study based on our recent experiences with subsequent cyclisation of the *o*-allenyl enol.[3] Here we report the results of this investigation.

The starting materials, 1,3-dimethyl-5-(prop-2-ynyloxy)-uracils (**3a–d**) were prepared in 88–94% yields by the alkylation of 1,3-dimethyl-5-hydroxyuracil[4] **1** with various prop-2-ynylic halides (**2a–d**) in refluxing acetone in the presence of anhydrous potassium carbonate (Scheme 1).



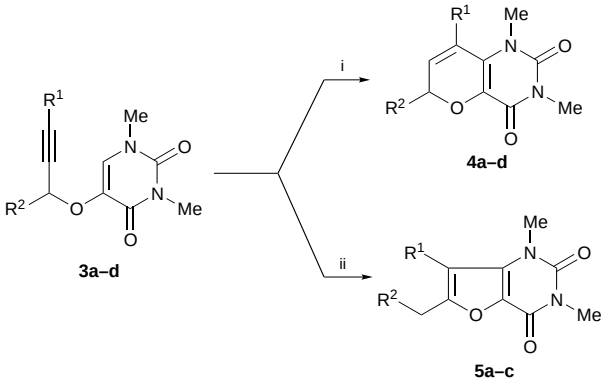
1 2 3

2,3	X	R^1	R^2
a	Br	H	H
b	Br	H	Me
c	Cl	CH_2OH	H
d	Cl	CH_2Cl	H

Scheme 1 *Reagents and conditions:* i, Me_2CO–K_2CO_3, reflux

The 1,3-dimethyl-5-(prop-2-ynyloxy)uracil **3a** was refluxed in purified chlorobenzene (bp 132 °C) to give 1,3-dimethyl-6*H*-pyrano[3,2-*d*]pyrimidine-2,4(1*H*)-dione **4a** as a white crystalline solid (88% yield), mp 202 °C. Other substrates (**3b–d**) were also similarly treated to furnish products (**4b–d**) in 90–94% yields (Scheme 2).

The exclusive formation of products **4a–d** from the ethers **3a–d** is explicable[4] by a [3s,3s] sigmatropic shift of the propynyl vinyl ether moiety of substrates **3a–d** followed by enolisation, a 1,5-H shift and electrocyclic ring closure to give **4a–d**. The ethers **3a–d** were also heated in basic solvents, *e.g.*, *N*,*N*-diethylaniline at 115 °C for 1.5 h to give exclusively the furo[3,2-*d*]pyrimidine-2,4(1*H*)-diones (**5a–c**) in 80–90% yields (Scheme 2). This conversion may also be completed in boiling pyridine (1.5 h). Substrates **3d** showed a tendency to decompose when heated in *N*,*N*-diethylaniline and no tractable product could be obtained. A mixture of products **4** and **5** was obtained when the reaction was conducted in chlorobenzene in the presence of a small amount of *N*,*N*-diethylaniline. The ethers decomposed completely when heated in chlorobenzene in the presence of toluene-4-sulfonic acid. The formation of product **4** was unaffected when a radical initiator, azoisobutyronitrile (AIBN), was added to the reaction mixture.



Scheme 2 *Reagents and conditions:* i, PhCl, reflux; ii, $PhNEt_2$, 115 °C

Only the one example each of the furo[3,2-*d*]pyrimidine-dione **5a** and the 6*H*-pyrano[3,2-*d*]pyrimidinedione **4a** in a mixture of varying amounts was reported earlier by Otter *et al.*,[2] the maximum yields reported for the compounds from different experiments being only 49% for **4a** and 66% for **5a**. The simple reaction conditions reported here seem to be general, as a number of furo- and pyrano-pyrimidines have been synthesised regioselectively in excellent yields, in each case exclusively one product being obtained. In addition the dimer of **4a** reported by Otter *et al.* was not detected in the reaction mixture.

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Techniques used: UV, IR, ^{1}H NMR, mass spectrometry

References: 5

Schemes: 2

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