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Studies on Uracils: Synthesis of Tetrazolo[4′,5′:1,6]pyrido[2,3-*d*]pyrimidines by the Action of Cyano Stabilised Carbanions on 6-Azido-5-formyluracils†

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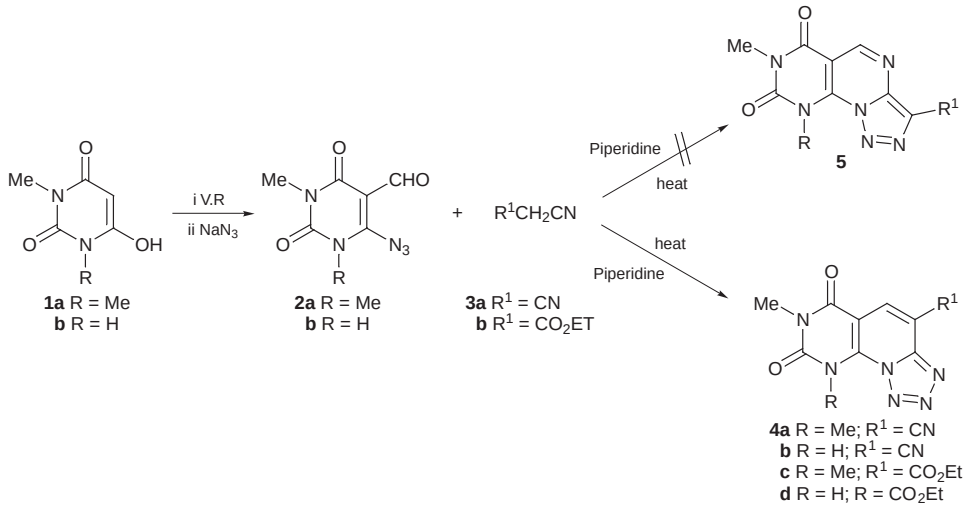
6-Azido-5-formyluracils **2** undergo base catalysed condensation with cyanocarbanions to yield tetrazolo[4′,5′:1,6]-pyrido[2,3-*d*]pyrimidines **4** in good yields.

The importance of uracil and its annelated substrates is well recognised by synthetic[1] as well as biological chemists.[2] With the development of clinically useful anticancer (5-flurouracil)[3] and antiviral drugs (AZT, DDC, DDI, BVDU),[4] there has recently been remarkable interest in the synthetic exploitation of uracils.

The attack of cyano stabilised carbanions on azide functions leading to 1,2,3-triazoles is a well known phenomenon in organic synthesis, and a number of reports are available in the literature.[5] An extensive study[6] of this process showed that aryl azides bearing a variety of *ortho*-substituents undergo solvent dependent intramolecular 1,3-dipolar cycloaddition reactions. Thus aryl azides with *ortho* substituents that possess electrophilic carbon sites undergo cyano stabilised carbanion attack in protic solvents to yield tetrazoloquinolines. Here we report the first example of this simple and effective cyclisation process for the synthesis of complex uracils. The reaction of 6-azido-5-formyluracils **2** with acetonitriles **3** (R^1CH_2CN) (Scheme 1) in the presence of piperidine in ethanol gave, in each case, a tetrazolo[4′,5′:1,6]pyrido[2,3-*d*]pyrimidine **4** in high yield.

3a and a catalytic amount of piperidine in ethanol was stirred at 40 °C for 30 min and then refluxed for 2 h. The solution was cooled to room temperature and the solid **4a** filtered off. This was then purified by column chromatography using chloroform–ethyl acetate as eluent. The yield of **4a** was 70%. Although there was a possibility of the formation of triazolo fused uracils **5** by the initial attack of the acetonitrile on the azido function followed by the condensation of the amine to the aldehyde group, we did not observe any such product. ^{1}H NMR spectroscopy of **4a** showed that the isolated proton at δ 8.05 is of the tetrazolo fused pyrido[2,3-*d*]pyrimidines **4a** and is not an imine proton of a triazolo fused pyrimido[4,5-d]pyrimidine. The presence of the cyanide group is confirmed from an IR band at 2230 cm^{-1}. Compounds **4b-d** were similarly prepared and their structures have been confirmed *via* spectroscopic data and elemental analyses. The absence of a cyanide band in IR spectra of products **4c**,**d** indicate the involvement of the nitrile function in the cyclisation process. From the CHN elemental analyses data of all the compounds **4a–d** it is confirmed that there are no loss of



Scheme 1 V.R = Vilsmeier reagent

In a simple experimental procedure an equimolar amount of uracil analogue **2a** (readily obtained from the corresponding barbituric acid **1a** by the action of Vilsmeier's reagent followed by sodium azide treatment), acetonitrile derivative nitrogen under the reaction conditions, and thus the products are as depicted in Scheme 1.

Although we could not isolate any intermediates, a reasonable mechanism for the reaction is outlined in Scheme 2. The reaction may occur by an initial Knoevenagel condensation at the aldehyde function followed by an intramolecular 1,3-dipolar cycloaddition of the azide function at the pendant cyano group of the sterically favoured cinamonitrile derivative.

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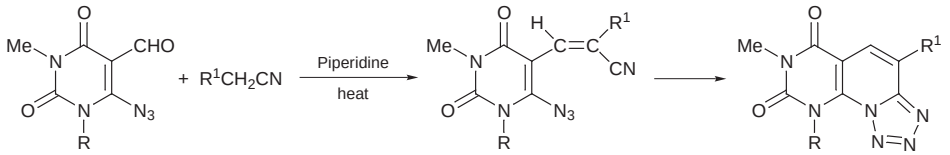
In conclusion, our results demonstrate a simple and effective cyclisation process for the synthesis of novel uracils of biological importance. Furthermore we have shown that attack of cyano stabilised carbanions on azide functions leading to tetrazolo fused derivatives of the parent molecule is applicable to heterocyclic compounds.

Caution. All the azides are potentially explosive and should not be heated as neat solids or liquids. All reactions involving azides described in this paper were carried out in solution.



Scheme 2

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Experimental

Mps were determined in open capillary tubes on a Buchi apparatus and are uncorrected. The 300 MHz ^{1}H NMR spectra were recorded in a Avanee DPX300 spectrometer with $CDCl_3$ as solvent and tetramethylsilane (TMS) as the internal standard. The IR spectra were recorded on a Perkin-Elmer 237B IR spectrometer as KBr discs. Elemental analyses were performed on a Hitachi 026 CHN analyser. 6-Azido-5 formyl uracils **2** were prepared by following standard procedures.[7,8]

General Procedure for the Synthesis of Tetrazolo[4′,5′:1,6]*pyrido*-[2,3-d]*pyrimidines* **4**.—To a mixture of 0.418 g (2 mmol) of 6-azido-5-formyl uracil derivative **2a** and 0.132 g (2 mmol) of malononitrile **3a** in ethanol was added two drops of piperidine. The mixture is initially warmed at 40 °C with stirring for 30 min and then refluxed for 2 h. The solution was then concentrated and cooled. The solid compound was filtered off and purified by column chromatography using chloroform–ethyl acetate (1:1) as eluent. The yield of **4a** was 0.360 (70%). Mp 285 °C. IR; 2230, 1695 cm^{-1}.δ_H ($CDCl_3$) 315 (s, 3H), 3.25 (s, 3H), 8.05 (s, 1H). Elemental analyses. Found: C, 46.60; H, 2.68; N, 38.15. Calc.: C, 46.69; H, 2.72 N, 38.13%. Compounds **4b**–**d** were similarly prepared. **4b**: yield 68%. Mp > 300 °C. IR; 2225, 1700 cm^{-1}. δ_H ($CDCl_3$) 3.20 (s, 3H), 8.10(s, 1H). Elemental analyses. Found: C, 44.40; H, 2.10; N, 40.28. Calc.: C, 44.44; H, 2.05; N, 40.32%. **4c**: yield 65%. Mp 276 °C. IR; 1735, 1695 cm^{-1}. δ_H ($CDCl_3$) 3.15 (s, 3H), 3.30 (s, 3H) 1.50 (t, 3H), 4.50 (q, 2H), 8.00 (s, 1H). Elemental analyses. Found: C, 45.17; H, 4.15; N, 28.70. Calc.: C, 45.20; H, 4.11; N, 28.76%. **4d** yield 60%. Mp > 300 °C. IR; 1730, 1700 cm^{-1}. δ_H ($CDCl_3$) 3.25 (s, 3H), 1.45 (t, 3H), 4.45 (q, 2H), 8.10 (s, 1H). Elemental analyses. Found: C, 43.15; H, 3.50; N, 30.25. Calc.: C, 43.16; H, 3.59; N, 30.21%.

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