Pergamon

Tetrahedron Letters, Vol. 37, No. 11, pp. 1853-1854, 1996

0040-4039/96 $15.00 + 0.00

S0040-4039(96)00134-7

"Tertiary Amine Effect" Strategy in the Synthesis of Novel Uracil Analogues

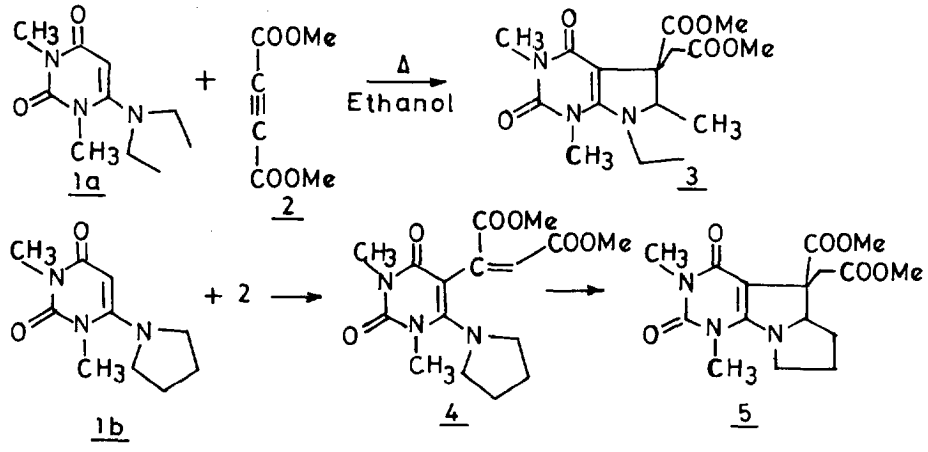
Pulak. J. Bhuyan, Jagir S. Sandhu* and Anil C. Ghosh

Regional Research Laboratory, Jorhat 785 006, Assam, India

ABSTRACT: 6-Tertiary amino uracils 1 react with dimethyl acetylenedicarboxylate 2 to give 4,5-dihydropyrrolo[2,3-d]pyrimidine 3 and 4,5,6,7,8-pentahydropyrrolizino[2,3-d]pyrimidine analogues 5 in excellent yields.

The importance of uracils and its annelated substrates is well recognised by synthetic[1] as well as biological chemist[2]. As a result of this effort, synthesis of numerous uracil based molecules, active against cancer and virus, has been achieved and several of these compounds are in clinical practice e.g. AZT, DDC, BVDU.

α–Cyclisation of tertiary amines is a mechanistically intriguing and synthetically useful cyclisation which has not received much attention. Certain tertiary anilines or enamines and enamine esters undergo such cyclisation leading to annulated pyrrolidines. Suschitzky and Meth-Cohn have coined the term "tertiary amine effect" for such processes which have been further developed by Reinhoudt and Verboom[3].



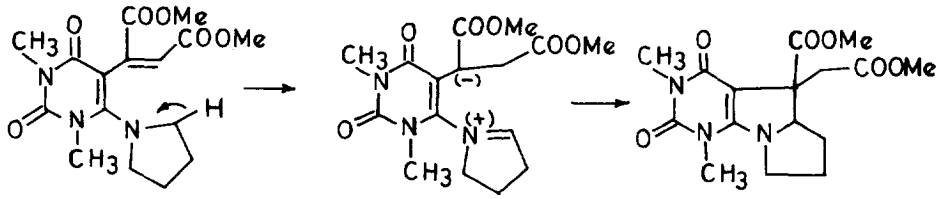
1a 2 3

1b 4 5

In the present paper we report the first application of "tertiary amine effect" in the synthesis of novel uracils. The reaction of N,N-dimethyl-6-diethylaminouracil **1a** and dimethyl acetylenedicarboxylate[4] **2** under thermolytic conditions gave the 4,5-dihydropyrrolo[2,3-d] pyrimidine analogue **3** in 85% yield. The N,N-dimethyl-6-pyrrolidino uracil 1b reacts in a similar

way to give 4,5,6,7,8-pentahydropyrrolizino[2,3-d]pyrimidines **5** in 80% yield. In a simple experimental procedure equimolar amounts of **1a** and **2** are refluxed in ethanol for 6h. The solvent was removed under reduced pressure and the residue upon washing with solvent ether gave the product **3.** Interestingly when the 6-cyclicaminouracil **1b** is reacted with DMAD at room temperature it gave a compound, which is identified as the simple Michael adduct **4**. This intermediate on refluxing in ethanol for 8 h gave the cyclised compound **5**. The structures of all the compounds have been confirmed spectroscopically.

It is evident from the intermediate that the reaction occured via initial Michael addition of DMAD at C-5 atom of the pyrimidine ring to give an aminodiene system **4**, which on subsequent heating, undergoes an internal redox process to generate a 1,5-dipole through a hydrogen shift, followed by ring closure to give the cyclised product **5** (Scheme).



4 Scheme 5

Although we have not determined the stereochemistry of the product, the 1,5-dipole might have cyclised in a favourable endo fashion when cyclic amines are employed and exo fashion when bulky acyclic tertiary amines are used.

In summary the thermal α-cyclisation of 6-tertiary aminouracils, leads to novel functionalised uracils in excellent yields.

References and Notes :

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(*Received in UK* 16 *October* 1995; *accepted* 26 *January* 1996)