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MICHAEL ADDITION OF 4-O-ETHYLURACIL. A METHOD FOR SPECIFIC N_1-ALKYLATION OF HYDROXYPYRIMIDINES.[1]

A.J.H. Nollet[2] and U.K. Pandit[3]
Laboratory for Organic Chemistry, University of Amsterdam,
Nieuwe Achtergracht 129, Amsterdam, The Netherlands.

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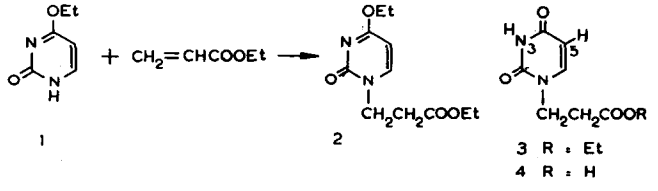
Current interest in the synthesis of nucleotide-components and their analogues has led to the quest for new methods of specific N_1-alkylation of uracil and related pyrimidine derivatives, in this laboratory. The N_1-cyanoethylation of uracil has been previously reported [4,5], but the conditions employed for the reaction were highly specific and subtle variations diverted the course of the reaction to N_1,N_3-dialkylation.

In order to develop a procedure which would unambiguously give the mono N_1-alkylated product and moreover, be capable of general application, we have examined the reaction of 4-ethoxy-2-keto-1,2-dihydropyrimidine (1) with ethyl acrylate - a typical electrophilic olefin. Refluxing a mixture of 1 and ethyl acrylate in ethanol, in presence of a trace of sodium ethoxide, gave indeed a high yield (80%) of the Michael-adduct 2. Since 1 is readily available [6] and, the heterocyclic system, following alkylation, can be conveniently converted into uracil or cytosine, the principle embodied in the reaction may be recognized as a simple general procedure for specific N_1-alkylation of hydroxypyrimidines.

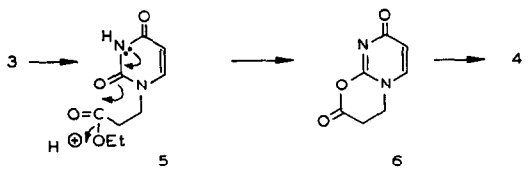


1 2

3 R : Et
4 R : H

Hydrolysis of 2 with dil. HCl, at room temperature, cleaved both the ether and, somewhat surprisingly, the ester functions, resulting in the formation of acid 4.

Structure of 4 followed from its spectroanalytical data; a salient point in the NMR spectrum (DMSO-d_6) being a coupling between the H_3 and H_5 protons (J=2 c/s), attesting to N_1-substitution [7]. The instability of 3 in dilute acids was confirmed by the observation that an authentic sample of 3 (prepared via esterification of 4) underwent hydrolysis in 1N HCl, at room temperature, with a half-life of less than 4 hours. The origin of this extraordinary lability presumably resides in the intramolecular catalysis of the ester-cleavage process, as depicted in 5. The intermediate 6, formed in the first step, would be expected to undergo a rapid hydrolysis, to 4, under the conditions of the reaction.



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1. This may be regarded as Part IV of the series "Unconventional Nucleotide Analogues". For Part III see A.J.H. Nollet and U.K. Pandit, Tetrahedron, in press.
2. Taken in part from the forthcoming doctorate dissertation of A.J.H. Nollet, University of Amsterdam.
3. To whom all correspondence should be addressed.
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