Studies on uracils: a facile one-pot synthesis of pyrazolo[3,4-d]pyrimidines

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Abstract—The reaction of 6-hydrazino uracils 1 with isocyanates 2 gave access to an efficient one-pot synthesis of pyrazolo[3,4-d]pyrimidines 3 in excellent yields. © 2002 Elsevier Science Ltd. All rights reserved.

The importance of uracil and its annelated derivatives is well recognised by synthetic as well as biological chemists. Pyrazolo[3,4-d]pyrimidines are a class of naturally occurring fused uracils that possess a wide range of biological activity. Allopurinol (6-dehydroxy-pyrazolo[3,4-d]pyrimidine), an effective xanthine oxidase inhibitor, is in clinical use for controlling gout and related metabolic disorders. Furthermore, the allopurinol 1-ribo-nucleotide-like 6-azauridine-5'-phosphate is a potential antiviral and antitumor agent. Several reports are available which suggest that 4-aminopyrazolo[3,4-d]pyrimidine nucleosides and related compounds may function as substrates for anabolic and catabolic enzymes. The discovery of strong antiparasitic properties shown by allopurinol, its 1-β-D-ribose derivative and related compounds has resulted in extensive work in this area, which has been reviewed. However, a literature survey revealed only a few reports on the synthesis of the parent pyrazolo[3,4-d]pyrimidine moiety, which usually requires drastic conditions, long reaction times and complex synthetic pathways.

Synthetic exploitation of the nucleophilic double bond of uracils is an important field in view of a great variety of potential products. Recently, we reported a novel method for the synthesis of pyrimido[4,5-c]pyrazidines from the reaction of 6-hydradino uracils and acetylene dicarboxylates at room temperature. In the present communication we describe the results of our study of the reaction of 6-hydradino uracils and isocyanates, which gives access to an efficient one-pot synthesis of pyrazolo[3,4-d]pyrimidines and thus a novel class of 3-amino-pyrazolo[3,4-d]pyrimidines in excellent yields.

A previous synthesis of pyrazolo[3,4-d]pyrimidine reported by Yoneda et al. involved the cycloaddition of the azahexatriene obtained from the reaction of an arylaldehyde and a 6-uracil hydrazone. One disadvantage of this approach is the concomitant arylation of the pyrazolo moiety. Earlier this class of compounds was synthesised by fusion of 6-uracil hydrazones at 300°C. Another synthesis reported by Maki et al. required the cycloaddition of an arylhydrazone with 6-chloro-5-nitro uracil, which involved several steps. Further, Kanazawa et al. synthesised pyrazolo[3,4-d]pyrimidines by the reaction of 6-aryledinehydrazinouracils with NBS (N-bromosuccinimide) in acetic acid under refluxing conditions, which yielded triazino and pyridazinouracils in addition to the pyrazolo[3,4-d]pyrimidines (Scheme 1).

Our synthetic strategy utilising 6-hydradino uracils 1 and isocyanates 2 affords an unprecedented one-pot

Scheme 1.
synthesis of pyrazolo[3,4-d]pyrimidines 3 in excellent yields.

In a very simple experimental procedure an equimolar amount of 1,3-dimethyl-6-hydrazino uracil 1a (0.170 g, 1 mmol) was added quickly to phenyl isocyanate 2a (0.119 g, 1 mmol) at room temperature. An exothermic reaction occurred. After 10 min the reaction mixture was refluxed in ethanol (10 ml) for 20 min. On cooling the thick precipitate of the product, which appeared in the compound was obtained and confirmed as 3a from spectroscopic data and elemental analysis, mp 246°C. 

\[ 1H \text{ NMR 90 MHz (CDCl}_3\text{TFA) } \delta 2.95 \text{ (s, 2H), 6.75 \text{–} 7.25 \text{ (m, 5H). 13C NMR 75 MHz (CDCl}_3\text{TFA) } \delta 28.0 \text{ (N}_3\text{-CH}_3\text{); 28.5 \text{ (N}_3\text{-CH}_3\text{); 107.0 \text{ (4a); (112.2, 114.2, 120.0, 123.7 aromatic); 129.6 (C-5); 158.2 (C-7a); 159.2 (C-2); 160.0 (C-4). IR 3230, 3220, 3205, 3190 cm}^{-1}. MS 271 M^+. CHN analyses (calcd %) C, 58.95; H, 4.75; N, 25.85.\]

Further study of this effective synthetic method is in progress. In conclusion, our results demonstrate a very simple and efficient method for the synthesis of well functionalised pyrazolo[3,4-d]pyrimidines of biological importance in excellent yields. Heteroannulation on the nucleophilic double bond of uracil, which is an important developing field for synthetic manipulation, usually requires either forcing conditions or relatively long and complex synthetic pathways. Our results delineated above have demonstrated that heteroannulation on the double bond of uracil is possible under simple and moderate conditions using suitable organic reagents such as isocyanates.

References


