Studies on Uracils. 10.[1] A Facile One-Pot Synthesis of Pyrido[2,3-*d*]- and Pyrazolo[3,4-*d*]pyrimidines

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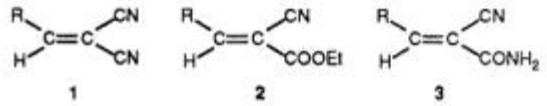
The reaction of functionalised uracils bearing amino and hydroxyamino groups at C-6 position (**4** and **5**) with strongly electrophilic cyano olefins (**1**, **2**, and **3**) gave rise to pyrido[2,3-*d*]pyrimidines **7–9** in excellent yields. Hydrazine-substituted uracil **6** gave access to an efficient one-step synthesis of pyrazolo[3,4-*d*]pyrimidines **10**. The capture of an eliminated hydrogen molecule by cyano olefins in the case of their reaction with **4** and **6** was confirmed by the isolation of dihydrocyano olefins. This fact further supported the plausible mechanism for the formation of compounds **7–10** via dihydropyrido[2,3-*d*]- and dihydropyrazolo[3,4-*d*]pyrimidine intermediates A and C.

The importance of uracil and its annelated substrates is well recognized by synthetic[2] as well as biological chemists.[3] With the development of clinically useful anticancer (5-fluorouracil[4]) and antiviral drugs (AZT,[5] BVDU[6]), there has recently been remarkable interest in the synthetic manipulations of uracils.[1,2,7] The synthetic exploitation of the nucleophilic double bond of uracil is an important undeveloped field in view of a great variety[8] of potential products. There have been reports for direct functionalization of uracil using the C_5–C_6 double bond via thermolytic[9] and photocycloaddition reactions.[10] The heteroannulation of uracils usually requires either forcing conditions[11] or relatively longer synthetic pathways.[12] The readily available cyano olefins are a class of important organic synthones having exciting chemistry.[13] In view of the considerable chemical reactivity of activated cyano olefins, we felt it would be valuable to investigate their reaction with strongly nucleophilic 6-amino-, 6-(hydroxyamino)-, and 6-hydrazinouracil (**4**, **5**, and **6**).

A previous synthesis for pyrazolo[3,4-*d*]pyrimidine reported by Yoneda et al.[11] involved the cycloaddition of azahexatriene obtained from the reaction of arylaldehyde and 6-uracil hydrazone. One disadvantage of this approach is the concomitant alkylation of the pyrazolo moiety. Another synthesis reported by Maki et al.[12] required the cycloaddition of arylhydrazone with 6-chloro-5-nitrouracil involving several steps. Broom et al.[14a] synthesized pyrido[2,3-*d*]pyrimidines from the reaction of DMAD and 6-aminouracil in protic solvent but obtained uncyclized condensed acetylenic adduct[14b] when the reaction was carried in dimethylformamide.

Our synthetic strategy utilizing cyano olefins viz arylidenemalononitrile (**1**), arylidenecyanoacetate (**2**), and arylidenecyanoacetamide (**3**) with **4**, **5**, and **6** afforded an unprecedented one-pot synthesis of pyrido[2,3-*d*]pyrimidines (**7–9**) and pyrazolo[3,4-*d*]pyrimidine (**10**).



1 2 3

R = **a**, Ph; **b**, 2-furyl; **c**, 2-thienyl

The activated cyano olefins **1**, **2**, and **3** were prepared by the knoevenagel condensation of malononitrile, ethylcyanoacetate, and cyanoacetamide with aromatic aldehydes.[15] The reaction of **4a** with an excess of **1a** in refluxing 1-propanol afforded 2-amino-6,8-dimethyl-5,7-dioxo-4-phenylpyrido[2,3-*d*]pyrimidine-3-nitrile (**7a**) and benzylmalononitrile in excellent yields. The products were fully characterized through spectral and elemental analysis. The IR spectra of **7a** exhibited sharp bands at 3435 and 3300 cm^{-1} (NH_2), 2195 (CN), and 1710 (C=O). The ^1H NMR spectrum showed singlets at δ 3.42 and 2.90 for *N*-methyl protons and a multiplet at δ 6.78–7.25 for aromatic protons. The mass spectrum gave a molecular ion peak at m/z 307. The structure of benzylmalononitrile was confirmed through comparison of spectral data and mixture melting point with an authentic sample.[22] It was

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