Novel Reactions of 5-Cyano-1,3-dimethyluracil. A Simple Synthesis of Pyrido[2,3-*d*]pyrimidines (1)

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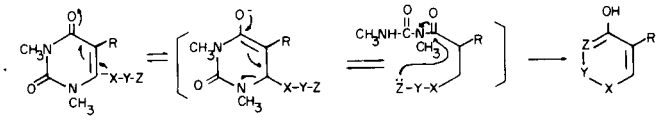
A reaction of 5-cyano-1,3-dimethyluracil (**1**, R = CN) with acetone in base afforded 1,3,7-trimethylpyrido-[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**9a**) in a moderate yield. From a reaction mixture of **1** (R = CN) with butanone, 1,3,6,7-tetramethyl- and 7-ethyl-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**9b** and **9c**, respectively) were isolated in low yields. When ethyl cyanoacetate or malononitrile was used in place of the ketone in the above reaction, 7-amino-6-ethoxycarbonyl- and 7-amino-6-cyano-1,3-dimethylpyrido[2,3-*d*]-pyrimidine-2,4(1*H*,3*H*)-dione (**14a** and **14b**, respectively) were obtained in *quantitative* yields. A plausible mechanism for the formation of bicyclic compounds is discussed.

J. Heterocyclic Chem., **19**, 1261 (1982).

Previously, we reported some novel ring transformation reactions in which the urea portion of 1,3-dimethyluracil derivative **1** is displaced by the N-C-N, C-C-N or C-C-C fragment of 1,3-ambident nucleophiles (X-Y-Z) leading to new pyrimidine (2), pyridine (3), or benzene (4) systems **4** *via* a Michael adduct **2** and an open-chain **3** intermediate. For the pyrimidine to benzene ring transformation using a ketone as the 1,3-ambident nucleophile, activation of the pyrimidine ring by introduction of an electron-withdrawing group (*e.g.*, NO_2) on C-5 is necessary.

Investigation of 5-cyano-1,3-dimethyluracil (**1**, R = CN) was of interest since, as in the nitro derivative **1** (R = NO_2), the 6 position is highly activated and would be susceptible to attack by even a soft nucleophile such as a ketone to form a Michael adduct **5** which might also undergo ring transformation to form a 2,4-dihydroxybenzonitrile **7** *via* an open-chain intermediate **6**. However, such was not the case. When **1** (R = CN) was treated with acetone in sodium ethoxide/ethanol, two products were obtained, one of which (12% yield) was identical with 1,3-dimethyluracil-5-carboxamide (**8**) (5) which arose from hydrolysis of the nitrile in **1**. The second product (18% yield) was identical with 1,3,7-trimethylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**9a**) (6). Apparently, the Michael adduct **5** was converted into the open-chain intermediate **6** which underwent cyclization by a mechanism involving attack by the terminal urea nitrogen on the cyano group to afford the 6-aminouracil intermediate **10**. Intramolecular condensation of the amino group with the neighboring ketone would furnish the formation of **9**.

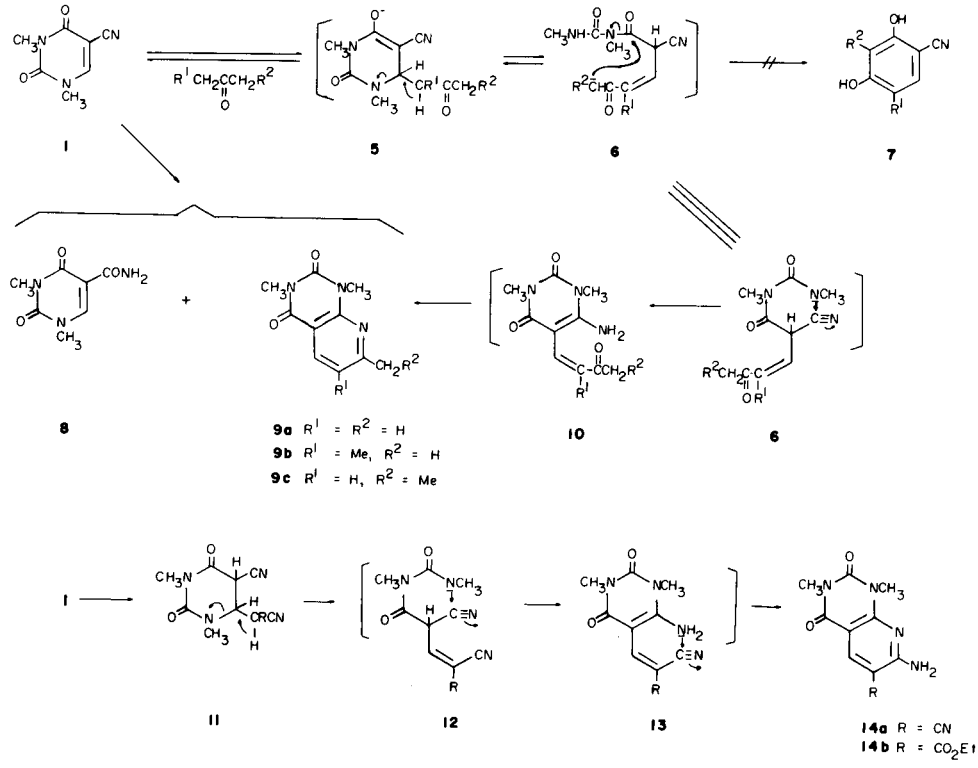


1 2 3 4

Treatment of **1** (R = CN) with butanone in base afforded two products, 1,3,6,7-tetramethyl- and 7-ethyl-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**9b**, and **9c** in 2% and 21% yield, respectively), in addition to **8** (9% yield). The structures of the bicyclic products were established by pmr spectroscopy: [For **9b** (deuteriochloroform): δ 2.34 (3H, s, CMe), 2.56 (3H, s, CMe), 3.47 (3H, s, NMe), 3.71 (3H, s, NMe) and 8.13 (1H, s, H-5); signals at δ 2.34 and 8.13 were slightly broadened due to allylic coupling; for **9c** (deuteriochloroform): δ 1.35 (3H, t, CH_2Me), 2.89 (2H, q, CH_2Me), 3.40 (3H, s, NMe), 3.73 (3H, s, NMe), 7.06 (1H, d, H-6, $J_{5,6}$ = 7.9 Hz), 8.31 (1H, d, H-5, $J_{5,6}$ = 7.9 Hz).

The mechanism proposed for the formation of **9** from **1** (R = CN) suggests that an activated acetonitrile, such as malononitrile or ethyl cyanoacetate, should form more readily the Michael adduct **11** since it is a better nucleophile than a ketone. The Michael adduct **11** should be converted more readily into the open-chain intermediate **12** since the α-proton of **11** is more acidic than that in **5**. Cyclization to the 6-aminouracil intermediate **13** and subsequent formation of the bicyclic product **14** should also occur readily. Actually, these expectations were confirmed by treatment of **1** (R = CN) with these reagents which afforded 7-amino-6-cyano-1,3-dimethylpyrido[2,3-*d*]-pyrimidine-2,4(1*H*,3*H*)-dione (**14a**), mp 352-353° [lit (7) mp 354°] and 7-amino-6-ethoxycarbonyl-1,3-dimethylpyrido-[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**14b**), mp 213-214°; [pmr (deuteriochloroform): δ 1.40 (3H, t, CH_2Me), 3.43 (3H, s, NMe), 3.60 (3H, s, NMe), 4.36 (2H, q, CH_2Me), 5.71 (1H, broad s, NH), 8.27 (1H, broad s, NH), 8.87 (1H, s, H-5)], respectively, in quantitative yield.

The procedure described herein should have wide applicability in the synthesis of a number of pyrido[2,3-*d*]-pyrimidines.



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REFERENCES AND NOTES

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