# A NOVEL AND FACILE SYNTHESIS OF PYRROLO[2,3-d]PYRIMIDINES

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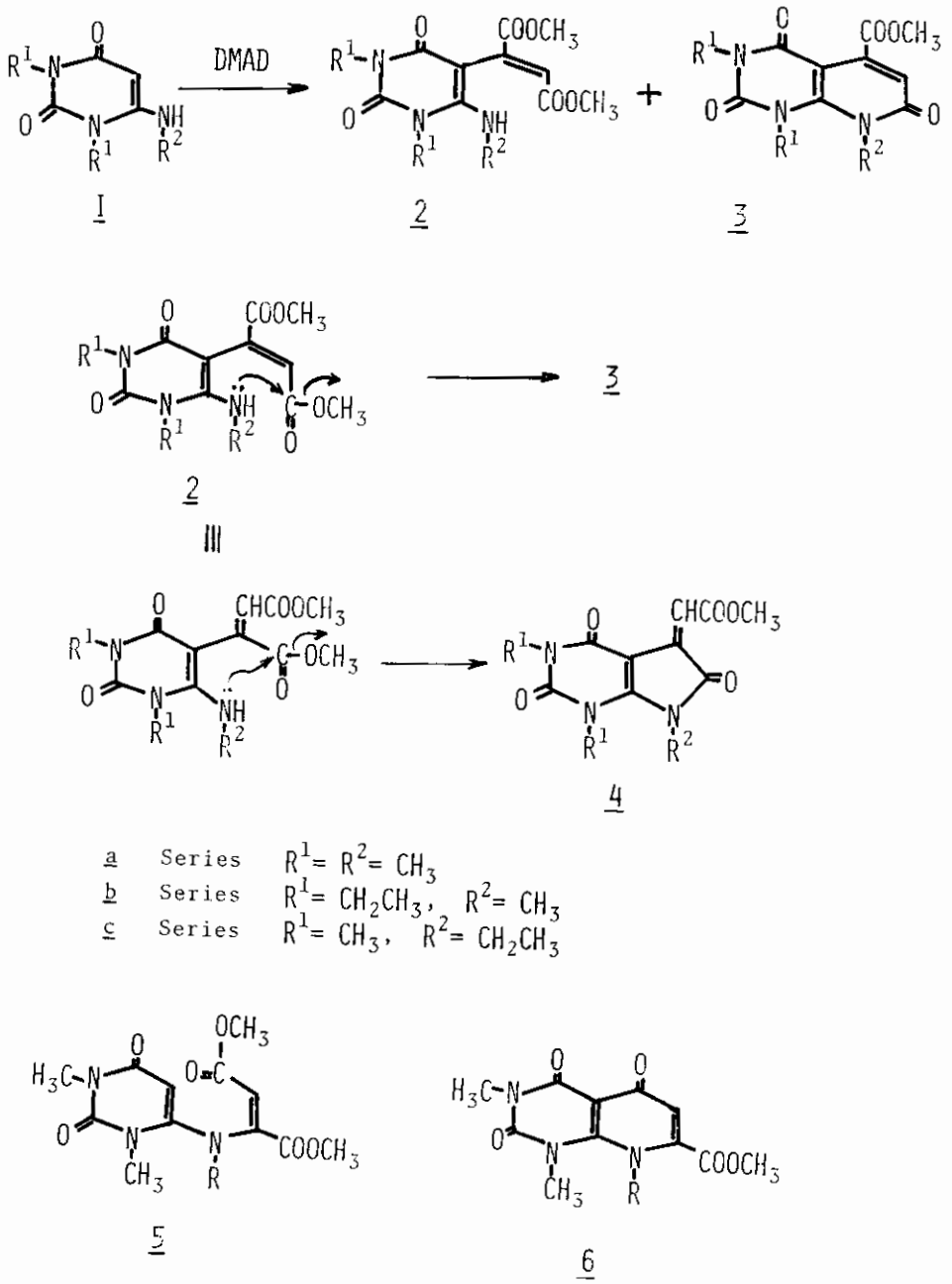
Abstract —— A novel two-step procedure for preparation of pyrrolo[2,3-d]pyrimidines is reported.

During the course of our research on the chemistry of pyrido[2,3-d]pyrimidines,[1] we found a novel and general method for preparation of pyrrolo[2,3-d]pyrimidines. Treatment of 1,3-dialkyl-6-alkylaminouracil (1) with dimethyl acetylenedicarboxylate (DMAD) in methanol at room temperature afforded dimethyl 2-(1,3-dialkyl-6-alkylaminouracil-5-yl)fumalate (2)[2] in 30 -40% yield together with small amount (1 - 8%) of 1,3,8-trialkyl-5-methoxycarbonylpyrido[2,3-d]pyrimidine-2,4,7(1H, 3H, 8H)-trione (3). Compound 3a is known,[3] and the UV spectral behaviors for 3b and 3c are very similar to those for 3a. The $^1$H NMR and mass spectral data (Table 1) and elemental analyses for 3b and 3c are also consistent with their structures. Assignment of the 5-substituted uracil structure (2) for the major products is made on the basis of the $^1$H NMR spectroscopy which showed these compounds to contain two methyl esters and one NH function in their molecules (Table 1). The mass spectral and analytical data also support this assignment.

Compound 2a was quantitatively converted into an 8:2 mixture of two isomers of which the minor product was the known pyridopyrimidine (3a)[3] by heating for 20 min at 165-175°C in an oil bath.

Previously it was reported[3] that a similar reaction of 1 ($R^1$=Me, $R^2$=H) with DMAD gabe a mixture of two isomeric products to which were given the pyrido[2,3-d]-

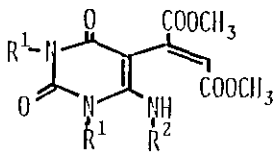
Chart 1



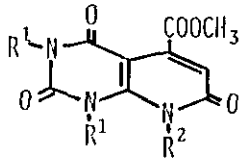

pyrimidine-2,4,7(1H, 3H, 8H)-trione (3) and -2,4,5(1H, 3H, 8H)-trione (6) structures on the assumption that the reaction would proceed through formation of two intermediates, 2 and 5.

The fact that both the major and minor products are derived from the same intermediate 2a disproved the involvement of 5 in the formation of the major product which, consequently, is not pyridopyrimidine 6. The only possible structure for the major product is 1,3,7-trimethyl-5-methoxycarbonylmethylidenepyrrolo[2,3-d]-pyrimidine-2,4,5(1H, 3H, 5H, 7H)-trione (4a). The most plausible mechanism for the formation for 4a from 2a is condensation of the α-carboxylate with the 6-alkylamino group as shown in Chart 1. In a similar manner, 2b afforded an 85:15 mixture of 4b and 3b, and 2c gave a readily separable 9:1 mixture of 4c and 3c.

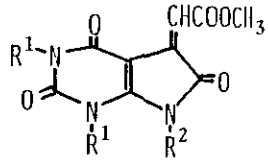
Table 1. Some physical properties for reaction products of 1,3-dialkyl-6-alkylaminouracil and dimethyl acetylenedicarboxylate.



2



3



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| Compd. | $R^1$ | $R^2$ | m/z($M^+$) | $^1H$ NMR ($CDCl_3$) chemical shifts: Me | $CH_2Me$ | -C=C<u>H</u>- | -N<u>H</u>-[a] |
|---|---|---|---|---|---|---|---|
| 2a | Me | Me | 311 | 2.70,[b] 3.25s, 3.43s | | 6.90s | 4.63 |
| 2b | Et | Me | 399 | 1.13t, 1.18t, 2.72d,[b] 3.66s, 3.82s | 3.82q 3.88q | 6.83s | 4.40 |
| 2c | Me | Et | 325 | 1.19t, 3.28s, 3.82s | 2.80-3.18m | 6.96s | 4.15-4.32 |
| 3a | Me | Me | 279 | 3.33s, 3.56s, 3.76s, 3.88s | | 6.70s | |
| 3b | Et | Me | 307 | 1.20t, 1.40t, 3.52s, 3.88s | 4.01q 4.28q | 6.72s | |
| 3c | Me | Et | 293 | 1.30t, 3.33s, 3.72s, 3.88s | 4.05q | 6.75s | |
| 4a | Me | Me | 279 | 3.33s, 3.47s, 3.72s, 3.82s | | | 7.17s |
| 4b | Et | Me | 307 | 1.23t, 1.40t, 3.47s, | 4.03q 4.27q | | |

[a]Exchangeable. [b]Collapsed to a singlet upon exchange with deuterium.

Treatment of 2 in refluxing methanol also afforded an 8:2 mixture of isomers. However, the major product was 3 and the pyrrolopyrimidine 4 was the minor product. Thus, the formation of pyrrolopyrimidine 4 requires more drastic conditions than does pyridopyrimidine formation. This is well expected since the five-membered ring in 4 is much more strained than the pyridone ring in 3.

The method developed for the synthesis of pyrrolo[2,3-d]pyrimidines should have a wide applicability in the preparation of various derivatives of purine analogs of biological interest.

REFERENCES AND FOOTNOTES

1) T. Itoh, T. Imini, H. Ogura, N. Kawahara, T. Nakajima and K. A. Watanabe, Heterocycles, 1983, 20, 2177; Chem. Pharm. Bull., 1985, 33, 1375.

2) A similar compound, 2 ($R^1$=$R^2$=H) has been isolated and characterized. A. D. Broon, J. L. Shim and G. L. Anderson, J. Org. Chem., 1976, 41, 1095.

3) H. Ogura and M. Sakaguchi, Chem. Pharm. Bull., 1973, 21, 2014.

Received, 23rd December, 1985