Part 4. Fused Pyrimidines. Annelation Using Formamide to Synthesize 2,4-Disubstituted-Pyrimido[4,5-*d*]Pyrimidines [1]

Thomas J. Delia* and Jill Niedzinski

Malcolm H. Filson Laboratories,
Department of Chemistry, Central Michigan University,
Mt. Pleasant, MI 48859

Received March 12, 1987

A one-step synthesis of 2,4-disubstituted-pyrimido[4,5-*d*]pyrimidines has been investigated. Cyclization of 6-amino-2,4-disubstituted-pyrimidines with formamide as solvent and reagent affords the title compounds in 50-70% yield. Strongly electron-donating groups are required. Based on model compounds, a pathway for the cyclization is suggested. The method is an improvement on previous methods of synthesis, albeit a limited one.

J. Heterocyclic Chem., **24**, 1421 (1987).

In connection with some studies of the chemical behavior of pyrimido[4,5-*d*]pyrimidines [2] we required samples of several 2,4-disubstituted derivatives. Most compounds of this class are prepared from pyrimidine precursors in which an amino function at position four is adjacent to a functional group at position five. Reports of suitable functional groups which participate in ring cyclization include the nitrile [3] and carboxamide [4]. Occasionally, a pyrimidine with an unsubstituted five position adjacent to an amino group has been successfully cyclized [5]. The annelation of a pyrimidine ring to a variety of existing rings has recently been reviewed by Albert [6].

Two of the three compounds we required, **2a,b**, had been prepared previously by Granados *et al.* [7] from the 5-bromopyrimidines, **1a,b** (X = Br). This reaction involved the addition of bromine to **1a,b** (X = H) in warm formamide, followed by heating for several hours at higher temperatures. Initially, this procedure was followed to obtain the samples for our earlier studies [2]. However, it soon became clear that the presence of the 5-bromo substituent served no useful purpose.

Subsequently, the 5-unsubstituted pyrimidines, **1a-c** (X = H) were treated with formamide at *ca.* 140-150°. In all cases the corresponding fused pyrimidines, **2a-c**, were obtained in fair yield. The products were identical to those prepared by established methods previously reported [7,8].

The ease with which these transformations occurred encouraged us to examine this process further. Both the scope and pathway were of interest to us.

The annelation of pyrimidine rings is most often accomplished with *pi*-excessive rings, although *pi*-deficient rings with strong electron donating groups may also serve as substrates [6]. The three examples which were successful in our hands each possessed three strongly activating groups in the 2-, 4-, and 6-positions. It was, therefore, of interest to see if other pyrimidines with less activation could be utilized in this reaction. A simple change involves replacing an amino function with a much weaker activating substituent such as the methyl group. Thus, 2,4-diamino-6-methylpyrimidine, **1d**, was subjected to the conditions previously used. Heating in excess formamide at approximately 150° for 5.5 hours failed to produce the corresponding pyrimido[4,5-*d*]pyrimidine, **2d**. The reaction was monitored by uv spectra and no change was noted, suggesting that no ring substitution occurred. However, concurrent examination of the reaction mixture by thin layer chromatography revealed the presence of a new product in addition to **1d**. Upon standing, a very small amount of this new substance could be obtained. Mass spectral analysis indicated a compound with a molecular ion of 152 and the ^{1}H nmr spectrum showed a proton at C-5. These results are consistent with an *N*-formyl derivative of **1d**. Formylation of aromatic amines by formamide has been observed [9]. Apparently the C-5 position has insufficient electron density to allow attack of a carbon electrophile. Since the methyl group is very weakly activating the presence of only two strongly activating groups appears to be insufficient. Steric factors were not seriously considered due to the similar size of the methyl and amino groups.

This compound allowed us to examine any possible role of the bromine which was reported in earlier syntheses [7]. The addition of bromine in formamide at 80° for 0.5 hour produced a significant uv shift of 12 nm. When the temperature was increased to 140° and maintained for 4 hours no further change in the uv spectrum was observed. The initial change in the maximum from 282 nm to 294 nm is consistent with the introduction of bromine into the 5-position of the pyrimidine. However, the pyrimido[4,5-*d*]-pyrimidine ring is characterized by a uv absorption band above 300 nm. Again, upon cooling of the reaction mixture, a small amount of product was obtained which had a molecular ion of 232/230. The ratio of these molecular ion values is consistent with a substance containing bromine. Furthermore, the numerical value indicates that both a

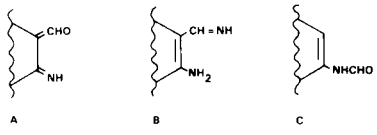
bromine and a formyl group are present. This experiment supports the contention that the original pyrimidine is not sufficiently activated to allow ring closure even though substitution by bromine is effected. Clearly, the presence of the bromine at C-5 does not enhance the reactivity.

One further experiment was attempted to ascertain whether the position of the activating groups was important. Thus, 4,6-diaminopyrimidine, **1e** (X = H), was subjected to the same general conditions of excess formamide at 140°. The reaction mixture was monitored by both uv spectra and tlc. No reaction could be detected [10].

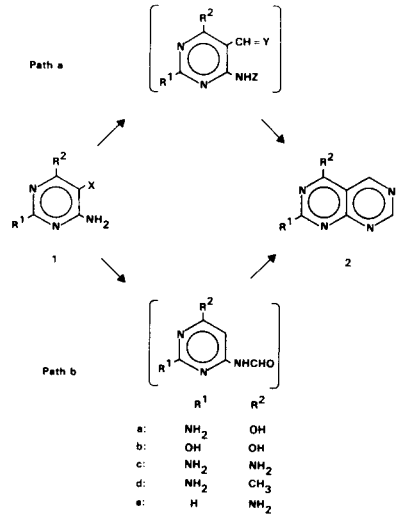
It is now clear that reaction with formamide requires three strongly activating groups. Therefore, this reaction is of limited generality in the preparation of pyrimido[4,5-*d*]pyrimidines, although the one step process represents an improvement over previous methods.

Our interest in the possible pathway of this reaction remained. While it is clear which pyrimidines would cyclize into the corresponding pyrimido[4,5-*d*]pyrimidines there remained the question of which intermediates were responsible.

In a previous study of the cyclization of 6-aminouracils with formamide three possible types of intermediates were postulated [11]. These are summarized as follows:



Of these alternatives only **C** represents a system in which initial attack does not occur at C-5. The substituents at C-5 in both **A** and **B** may be considered a variation of the carboxaldehyde group. However, in none of the experiments performed in the present study, including those which led to pyrimido[4,5-*d*]pyrimidines, was any intermediate detected or isolated in which a carbon fragment at C-5 was observed. If the reaction were proceeding through **path a** some evidence for a formyl group at C-5 should have been seen. To confirm that such a C-5 substituted pyrimidine would lead to a cyclized product **1a** (X = CHO) was heated in formamide with the rapid formation of **2a**. Thus, any 5-formyl derivative would cylize very rapidly upon formation and probably not be seen by the spectroscopic methods used in this study. However, *N*-formylation was demonstrated for several pyrimidines which did not lead to pyrimido[4,5-*d*]pyrimidines. These observations suggest that **path b** is the more plausible one. Nevertheless, there is insufficient evidence to conclude that **path b** is the correct one to the exclusion of **path a**.



EXPERIMENTAL

All ^{1}H nmr spectra were recorded either on a JEOL FX 90Q fourier transform spectrometer or a Bruker NR80 spectrometer in dimethylsulfoxide-d6 with tetramethylsilane as the internal standard. Mass spectra were measured on a Varian MAT-CH7 or a Hewlett Packard 5995A GC/MS, using the direct insertion probe method. UV spectra were recorded in aqueous solutions on a Unicam SP 1800 ultraviolet spectrophotometer or a Varian 2300 spectrophotometer. Thin Layer Chromatography was performed on silica gel with a 4:1 mixture of ethyl acetate:methanol as the eluting solvent.

General Method For Synthesis of Pyrimido[4,5-*d*]pyrimidines **2a-c**.

The following method is typical. Pyrimidine **1a** (X = H) (*ca.* 1 mmole) was heated in a 25 ml round bottom flask with formamide (5 ml at 150° for 8 hours. The course of the reaction was generally followed by uv spectra and tlc. The product was isolated upon cooling of the reaction mixture first to room temperature and then at 5°. The product was filtered, washed with methanol and dried, yield, 69%. The product, **2a**, was identical to that prepared according to earlier methods [7], as determined by uv, nmr and mass spectrum.

Pyrimidine **1b** (X = H) was similarly treated to give **2b** in 65% yield. In this case, however, 25 ml of water was added to the warm reaction mixture to induce precipitation of the product.

Pyrimidine **1c** (X = H) was similarly treated to give **2c** in 56% yield.

Acknowledgement.

This work was initiated in the laboratories of the Medical Chemistry Group, John Curtin School of Medical Research of the Australian National University in Canberra. The principal author remains indebted to Drs. D. J. Brown and W. L. F. Armarego for their interest and encouragement during these initial phases.

REFERENCES AND NOTES

[1] This work was presented, in part, at the 192nd ACS National Meeting, Anaheim, CA, September 1986.

[2] T. J. Delia, *J. Org. Chem.*, **49**, 2065 (1984).

[3] S. K. Chatterji and N. Anand, *J. Sci. Ind. Res.* (India), **18B**, 272 (1959).

[4] S. P. Gupta, R. K. Robins and R. A. Long, *J. Heterocyclic Chem.*, **12**, 1311 (1975).

[5] H. Bredereck, F. Effenberger and R. Sauter, *Angew. Chem.*, **72**, 77 (1960).

[6] A. Albert, *Adv. Heterocyclic Chem.*, **32**, 1 (1982).

[7] R. Granados, F. Marquez and M. Melgarejo, *An. R. Soc. Esp. Fis. Quim.*, Ser., **B58**, 479 (1962).

[8] E. C. Taylor, R. J. Knopf, R. F. Meyer, A. Holmes and M. L. Hoefle, *J. Am. Chem. Soc.*, **82**, 5711 (1960).

[9] B. C. Challis and A. R. Butler, in "The Chemistry of the Amino Group", S. Patai, ed, Interscience Publishers, New York, 1968, pp 289-290.

[10] We prepared 4-aminopyrimido[4,5-*d*]pyrimidine, **2e**, as a reference compound according to the method of Taylor [8] in which 4-amino-5-cyanopyrimidine was treated with formamidine acetate. A second procedure using the same pyrimidine and formamide has been reported to form **2e**. However, in our hands no **2e** could be observed in the reaction mixture.

[11] H. Bredereck, F. Effenberger and R. Sauter, *Chem. Ber.*, **95**, 2049 (1962).