FUSED PYRIMIDINES

Part Four

Miscellaneous Fused Pyrimidines

Thomas J. Delia

Department of Chemistry
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Mt. Pleasant, Michigan

With Contribution by

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Cambridge, Massachusetts

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Part Four

This is a part of the twenty-fourth volume in the series

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

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A SERIES OF MONOGRAPHS

EDWARD C. TAYLOR, *Editor*

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The Chemistry of Heterocyclic Compounds
Introduction to the Series

The chemistry of heterocyclic compounds constitutes one of the broadest and most complex branches of chemistry. The diversity of synthetic methods utilized in this field, coupled with the immense physiological and industrial significance of heterocycles, combine to make the general heterocyclic arena of central importance to organic chemistry.

The Chemistry of Heterocyclic Compounds, published since 1950 under the initial editorship of Arnold Weissberger, and later, until Dr. Weissberger's death in 1984, under our joint editorship, has attempted to make the extraordinarily complex and diverse field of heterocyclic chemistry as organized and readily accessible as possible. Each volume has dealt with syntheses, reactions, properties, structure, physical chemistry and utility of compounds belonging to a specific ring system or class (e.g., pyridines, thiophenes, pyrimidines, three-membered ring systems). This series has become the basic reference collection for information on heterocyclic compounds.

Many broader aspects of heterocyclic chemistry are recognized as disciplines of general significance which impinge on almost all aspects of modern organic and medicinal chemistry, and for this reason we initiated several years ago a parallel series entitled *General Heterocyclic Chemistry* which treated such topics as nuclear magnetic resonance, mass spectra, and photochemistry of heterocyclic compounds, the utility of heterocyclic compounds in organic synthesis, and the synthesis of heterocyclic compounds by means of 1,3-dipolar cycloaddition reactions. These volumes are of interest to all organic and medicinal chemists, as well as to those whose particular concern is heterocyclic chemistry.

It has become increasingly clear that this arbitrary distinction created as many problems as it solves, and we have therefore elected to discontinue the more recently initiated series *General Heterocyclic Chemistry*, and to publish all forthcoming volumes in the general area of heterocyclic chemistry in *The Chemistry of Heterocyclic Compounds* series.

EDWARD C. TAYLOR

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Preface

Three major works on the subject of fused pyrimidines including quinazolines, purines, and pteridines have been made available to the science community. There remain a variety of less well known fused pyrimidines that, nevertheless, deserve coverage. Part IV of Volume 24 completes the review of fused pyrimidines in which the second ring is six-membered and contains one or more of the elements of nitrogen, oxygen, or sulfur. Although other heteroatoms are found in the second ring of fused pyrimidines, as well as certain combinations of the three atoms mentioned above, the amount of literature available on these systems does not warrant a review at this time. No bridged heteroatoms are included in this volume.

Even though the subject of the pyridopyrimidines has been reviewed several times since the beginning of *Chemical Abstracts* it has been included here in the interest of completeness, although only from 1967. As can be seen from the 400 references since 1967, this subject and, to a lesser extent, the pyrimidotriazines have been popular ring systems for chemical investigation. This is not surprising because they are readily regarded as deaza- or azapteridines. The remaining topics, on the other hand, may be regarded as "orphan fused pyrimidines."

In keeping with the tradition established by the three previous parts of Volume 24, the text attempts to provide a critical survey of synthetic methods and reactions of each class of compound. This is followed by tables of individual compounds containing practical information such as melting points and spectral data.

Every attempt was made to provide coverage of each chapter at least through the end of the 1988 *Chemical Abstracts* volumes. However, not all of the literature may have been included either through oversight or because of the limited additional contributions to already described chemistry.

Any effort of this magnitude depends on many more people than the author. At the outset my appreciation goes to Dr. Des Brown for suggesting that I undertake this project and for his encouragement during the period of gestation. Professor E. C. Taylor also provided encouragement throughout the period of writing but, even more importantly, allowed me to spend time in his laboratory at Princeton University in order to facilitate completion of the manuscript.

My gratitude goes also to David Ginsburg, science librarian at Central Michigan University, for his cheerful, enthusiastic, and essential assistance in acquiring the necessary information through his skills with CAS ONLINE.

During the final phase of this effort, John Warner, who was a graduate student at Princeton University, enthusiastically volunteered to collaborate with me on a subject that he knew very well, the pyridopyrimidines. I extend my

appreciation to him for his contribution and he, in turn, acknowledges the assistance provided to him by Lloyd D. Taylor (of Polaroid Corporation) and by Natalie Warner.

Finally, my children Sarah, Cathy, Frank, and Alice, and especially my wife Sarah, are owed a debt of gratitude for their patience and encouragement as they suffered with me the torments of composing, editing, and proofing the manuscript.

THOMAS J. DELIA

Mt. Pleasant, MI
September 1991

Note to Reader

Although an effort has been made to have this monograph conform in style to the previous parts of Fused Pyrimidines, the nature of the subject makes this difficult, if not impossible. Whereas each of the first three parts dealt with a single ring system this book covers six distinct ring systems. Hence, each chapter is presented as a complete entity, including separate tables and references. The indexes will, however, be collected from all of the chapters.

Because each chapter deals with separate chemical ring systems one is at the mercy of the type of literature that is available. For this reason there are differences even within the way different fused pyrimidines are presented. This is seen by the variety of approaches illustrated in the tables of contents for the six chapters.

Each chapter begins with a brief section dealing primarily with nomenclature. Examples are illustrated and the naming of the specific rings are in accord with IUPAC rules, especially as they apply to fused heterocycles. After this brief introduction each chapter follows the format of synthetic methods first and then reactions. Where it has been considered helpful, or the volume of material too large, isomers have been treated separately within the discussion. A section on patents is included at the end of the discussion. No attempt has been made to be comprehensive here. Rather, the aim is to indicate how much patent interest there has been in the heterocycle as well as to show the types of compound available exclusively through the patent literature. It is assumed that the reader will conduct a more thorough search of the patent literature where there is sufficient interest.

This is followed by lengthy tables, which require further comment. It was felt desirable to provide the reader with tables containing simple headings so that compounds with certain features would be more accessible. Since the majority of compounds were collected through CAS ONLINE, the preferred *Chemical Abstracts* nomenclature was available for each of the compounds. In many cases this would have created awkward listings, which would not have been grouped by either functional group or other distinguishing features. Therefore, the names of the compounds have been altered slightly from those preferred by *Chemical Abstracts* and placed in alphabetical order within each table or section of a table. Any errors in naming or in alphabetizing are due to the author and apologies are extended to the reader for any inconvenience this may cause. Again, no attempt was made to include every compound in the tables. Only compounds that have been reasonably well characterized were selected for inclusion. The reader will undoubtedly perform an independent literature search for specific needs. Compounds that are found only in the patent literature are not included.

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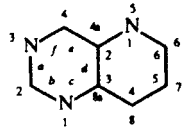
Contents

CHAPTER I

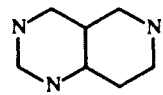
Pyridopyrimidines*

1. INTRODUCTION

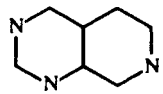
This chapter deals with four possible isomeric structures for pyridopyrimidines. The method of naming and numbering the ring systems is illustrated for structure **1**, the pyrido[3,2-*d*]pyrimidines. The numbers on the outside of the ring indicate how substituents are defined. The numbers and letters on the inside of the ring depict how the ring system itself is described. The same designations apply to the other three isomers, **2**–**4**. These systems have also been named as triazanaphthalenes.



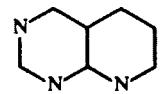
PYRIDO[3,2-*d*]PYRIMIDINE
1



PYRIDO[4,3-*d*]PYRIMIDINE
2



PYRIDO[3,4-*d*]PYRIMIDINE
3

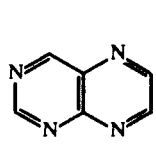


PYRIDO[2,3-*d*]PYRIMIDINE
4

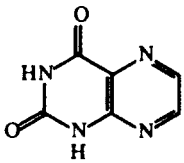
The literature up to the end of 1967 has been reviewed by Irwin and Wibberley[1] and since that time other reviews[2,3] have dealt with aspects of pyridopyrimidines. This chapter deals with the literature after 1967 concerning pyridopyrimidines with no additional ring fusions. The reader is advised to consult the other material in addition to this report for a complete overview of the chemistry and properties of these ring systems.

* By John C. Warner, Polaroid Corporation, Cambridge, Massachusetts.

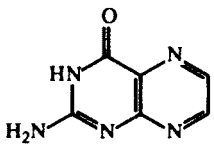
A great deal of chemistry has been investigated because of the similarity of pyridopyrimidines with pyrimido[2,3-*d*]pyrazines, which have been given the trivial name pteridines, **5**. Two trivial names for derivatives of pteridines are lumazine for pteridin-2,4-dione, **6**, and pterin for 2-aminopteridin-4-one, **7**. Various pyridopyrimidines have been referred to as some combination of deazapteridines, lumazines, or pterins.



PTERIDINE
5

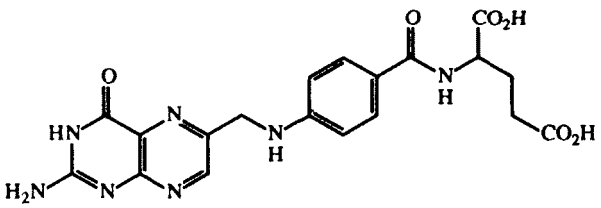


LUMAZINE
6



PTERIN
7

The synthesis and biological applications of derivatives of folic acid, **8**, have received a great deal of attention. The chemistry of these compounds has been the topic of a recent review[4] and thus has not been included in this chapter except to illustrate a specific synthetic approach or reactivity.



FOLIC ACID
8

2. METHODS OF SYNTHESIS OF THE RING SYSTEM

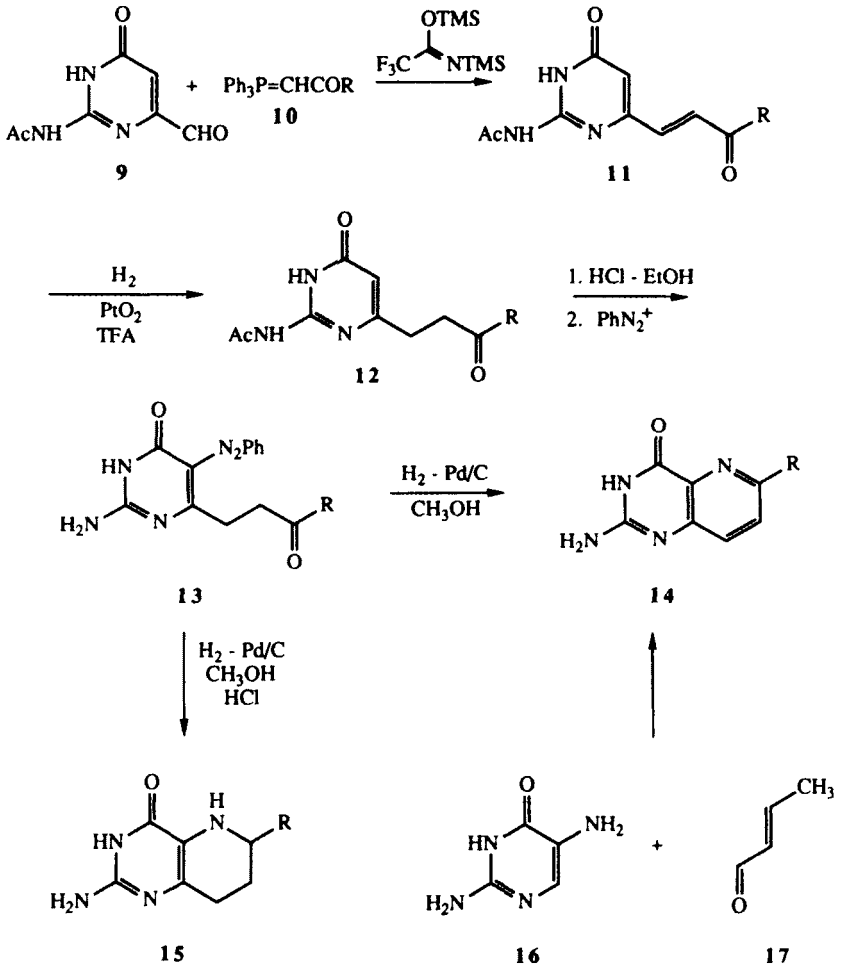
Syntheses of pyridopyrimidines fall into two categories. Syntheses may involve fusion of the pyridine ring onto the preformed pyrimidine ring, or they may involve fusing of the pyrimidine ring onto an already existent pyridine. Examples of both of these classes have been used for the synthesis of all four isomers. Because the position of the nitrogen in the pyridine ring alters the chemistry of these compounds and their precursors, the synthesis of each ring system has been dealt with independently.

A. Synthesis of Pyrido[3,2-*d*]pyrimidines

(1) *From Pyrimidines*

The nitrogen atom at position 5 of pyrido[3,2-*d*]pyrimidines has served as the site of reaction in most of the syntheses starting with pyrimidines. Pyrimidines containing the amino group or other nitrogen function at position 5 serve as substrates for elaboration of the pyridine ring. This approach is especially useful for the introduction of substituents at position 6 of the pyrido[3,2-*d*]pyrimidine.

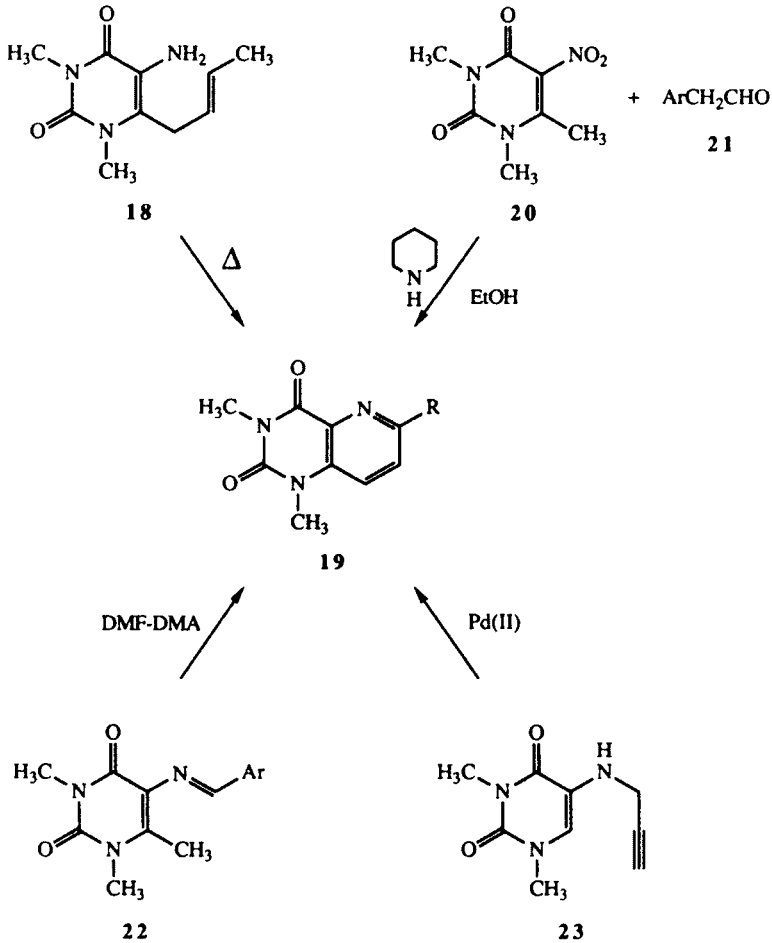
The condensation of 2-(acetylamino)-6-formyl-4-hydroxypyrimidine, **9**, with ketophosphonates, **10**, has given **11**, which was hydrogenated with platinum oxide as catalyst. Diazonium coupling of the 2-amino-(3-oxopropyl)pyrimidin-6-ones, **12**, to give **13**, followed by reductive ring closure has led to 2-aminopyrido[3,2-*d*]pyrimidin-4(3*H*)-ones, **14**.[5,6]



This reductive ring closure of **13**, when performed in the presence of acid, affords the 5,6,7,8-tetrahydropyrido[3,2-*d*]pyrimidine, **15**.[6]

It is not necessary to have a substituent at position 6 of the pyrimidine ring since 5-aminopyrimidines have been cyclized with various 1,3-bis-electrophiles to fuse the pyridine ring. The acid-catalyzed condensation of 2,5-diamino-4-pyrimidinone, **16**, with crotonaldehyde, **17**, for example, has been reported to give 2-amino-6-methylpyrido[3,2-*d*]pyrimidin-4(3*H*)one, **14** (R = Me).[9,10] When cinnamaldehyde was used in place of crotonaldehyde only uncyclized anil products were formed.

Another example of the cyclization of a functionalized side chain at position 6 of a 5-aminopyrimidine is found in the uracil series. 5-Amino-1,3-dimethyl-6-(substituted-allyl)-uracils, **18** (R = Me), prepared by Claisen rearrangement of 5-allylamino-1,3-dimethyluracils, are thermally cyclized to pyrido[3,2-*d*]pyrimidines, **19** (R = Me).[7]



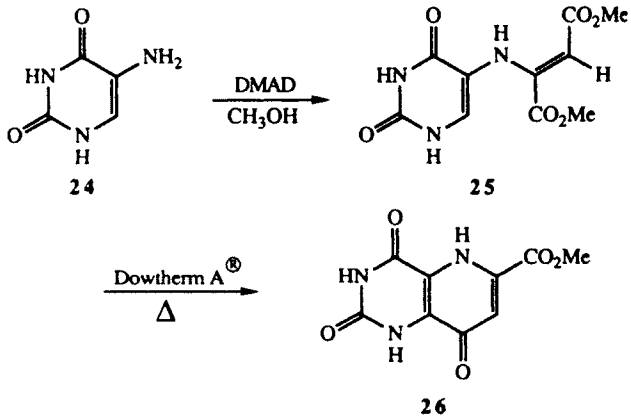
18 **20** **21** **19** **22** **23**

In a similar reaction, 6-aryl-1,3-dimethylpyrido[3,2-*d*]pyrimidin-2,4(1*H*,3*H*)-diones, **19** (R = Ar), have been synthesized via the condensation of 1,3,6-trimethyl-5-nitrouracil, **20**, with aryl acetaldehydes.[8] It is likely that the methodology is limited to 6-aryl derivatives because arylidine intermediates are formed.

A parallel reaction involves the cyclization of 5-arylideneamino-1,3,6-trimethyluracils, **22**, with *N*,*N*-dimethylformamide–dimethylacetal (DMF–DMA) to give the same 6-aryl-1,3-dimethylpyrido[3,2-*d*]pyrimidin-2,4(1*H*,3*H*)-diones, **19**, via 5-arylideneamino-1,3-dimethyl-6-(2-dimethylaminovinyl)-uracils.[8,12]

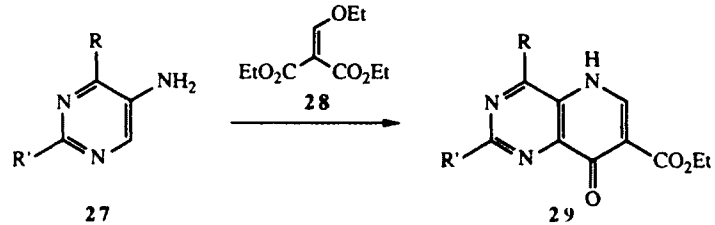
Finally, it is possible to synthesize this ring system in which there is no substituent at position 6. Palladium catalyzed cyclization of 1,3-dimethyl-5-(propargylamino)uracil, **23**, has led to **19** (R = H).[7]

Several interesting reactions have been described in which oxygen has been introduced into the pyridine ring. Michael addition of 5-aminouracil, **24**, to dimethyl acetylenedicarboxylate (DMAD) followed by thermal cyclization of the intermediate enamine, **25**, gives 6-(methoxycarbonyl)pyrido[3,2-*d*]pyrimidin-2,4,8(1*H*,3*H*,6*H*)-trione, **26**.[11] However, the scope of this reaction is limited by poor yields of most of the products obtained.



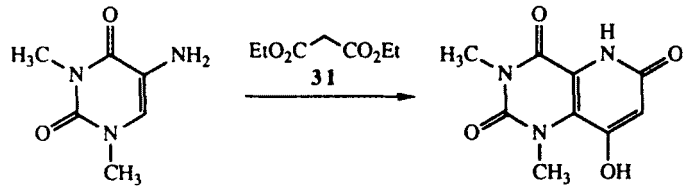
24 25 26

Somewhat better results have been obtained by the condensation of other 2,4-disubstituted-5-aminopyrimidines, **27**, with diethyl ethoxymethylene-malonate, **28**, as the 1,3-bis-electrophile. This reaction has been reported to give the isomeric 7-(ethoxycarbonyl)pyrido[3,2-*d*]pyrimidin-8(5*H*)-ones, **29**, although aryl derivatives are not possible in this case.[10]



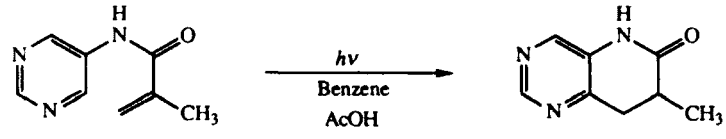
27 28 29

The reaction of 5-amino-1,3-dimethyluracil, **30**, with diethyl malonate, **31**, gave the dioxygenated pyrido[3,2-*d*]pyrimidine **32** at high reaction temperatures.[10] 5-Aminouracil and 5-amino-2,4-dimethoxypyridine failed to give pyrido[3,2-*d*]pyrimidines with this bis-electrophile.



30 **32**

The photolysis of *N*-(5-pyrimidyl)methacrylamide, **33**, in benzene with a catalytic amount of acetic acid has been reported to give 7,8-dihydro-7-methylpyrido[3,2-*d*]pyrimidin-6(5*H*)-one, **34**, in low yield.[13]



33 **34**

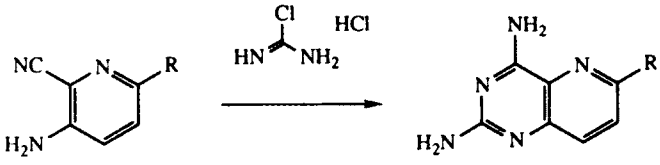
(2) *From Pyridines*

Most syntheses of pyrido[3,2-*d*]pyrimidines that involve fusion of a pyrimidine ring onto a pyridine ring begin with a 3-aminopyridine derivative. Treatment of 3-aminopyridine-2-carboxamide, **35**, with DMF–DMA, for example, gives the pyrido[3,2-*d*]pyrimidin-4(3*H*)-one, **36**.[14] Presumably, the use of appropriately substituted pyridines would lead to the formation of pyrido[3,2-*d*]pyrimidines with substituents in the pyridine ring, although this does not appear to have been explored.

35 **36**

Cyclizations of 3-aminopyridines having other substituents at the 2 position have been occasionally reported. Condensation of 3-amino-2-cyanopyridines, **37**, with chloroformamidine hydrochloride gives 2,4-diaminopyrido[3,2-*d*]py-

rimidines, **38**, by which a variety of substituents at position 6 can be introduced either directly or through subsequent nucleophilic displacement reactions.[15,16]



37 **38**

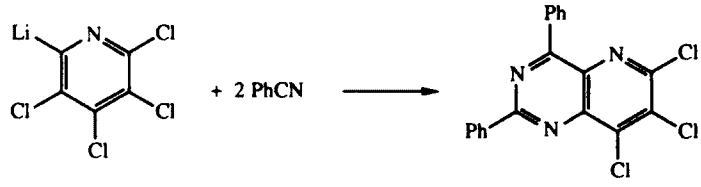
One of the more versatile precursors in this approach to pyrido[3,2-*d*]pyrimidines is 3-aminopicolinic acid, **39** (R = H). The condensation of **39** (R = H) with a variety of thiocyanates leads to the general structure **40**. Thus, ammonium thiocyanate leads to **40** (R′ = H; X = S) via thermolysis of a thiourea intermediate[18] and allylisothiocyanate in refluxing alcoholic solution gives **40** (R′ = allyl; X = S).[18]

The corresponding ester, **39** (R = Et), has also proven to be extremely useful. Condensation of this pyridine with heteroaroylazides has been shown to give 3-arylpyrido[3,2-*d*]pyrimidin-2,4(1*H*,3*H*)-diones, **40** (R′ = Ar; X = O), through uncyclized urea intermediates.[17] This method represents a unique way of introducing a hetero ring as a substituent onto the pyridopyrimidine ring.

Treatment of **39** (R = Et) with (ethoxycarbonyl)isothiocyanate gives a thiourea intermediate which, upon cyclization with sodium ethoxide, leads to the thio compound, **40** (R′ = H; X = S).[19] Other isocyanates or isothiocyanates behave similarly.[20,21]

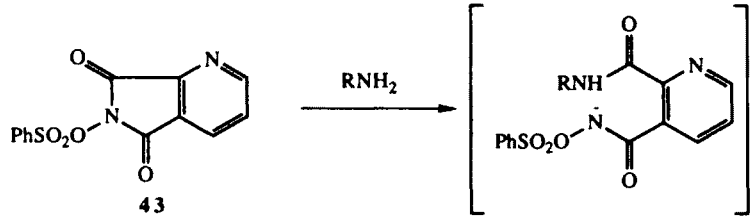
39 **40**

A synthesis that does not follow this general strategy of starting with a 3-aminopyridine is the reaction of tetrachloro-2-pyridyl lithium, **41**, with an excess of benzonitrile. This procedure has been reported to give 6,7,8-trichloro-2,4-diphenylpyrido[3,2-*d*]pyrimidine, **42**, through an *N*-lithio-imine intermediate.[22]



41 **42**

Finally, *N*-(phenylsulfonyloxy)quinolinimide, **43**, has been demonstrated to react with amine nucleophiles to give pyrido[3,2-*d*]pyrimidines, **45**, by fusion of the ring open intermediate, **44**.[23] Nucleophilic attack occurs at the more electrophilic carbonyl group followed by a Lossen-type rearrangement[24] to give only one regioisomer.



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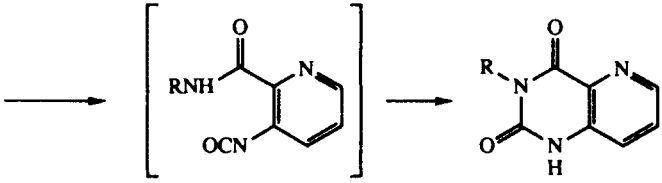


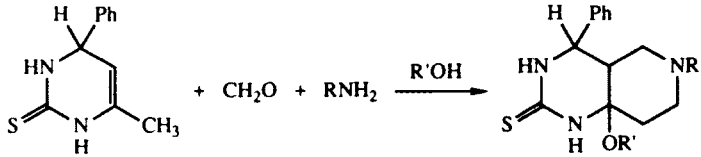
44 **45**

R = H, NH_2, OH, Ph

B. Synthesis of Pyrido[4,3-*d*]pyrimidines

(1) *From Pyrimidines*

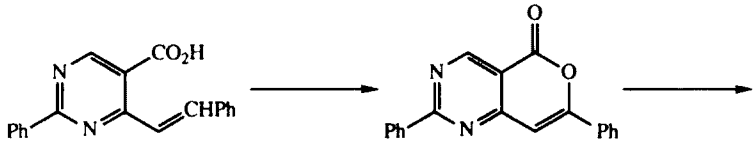
There are three general syntheses of pyrido[4,3-*d*]pyrimidines reported that begin with preformed pyrimidines. The cyclization of dihydropyrimidin-2-thiones, **46**, with primary amines and formaldehyde in a Mannich-type reaction gives 8a-alkoxy-3,4,4a,5,6,7,8,8a-octahydropyrido[4,3-*d*]pyrimidin-2(1*H*)-thiones, **47**.[25] This undoubtedly takes advantage of the labile hydrogens of the methyl group on the pyrimidine. The 8a-alkoxy group derives from covalent addition to the double bond between 4a and 8a.



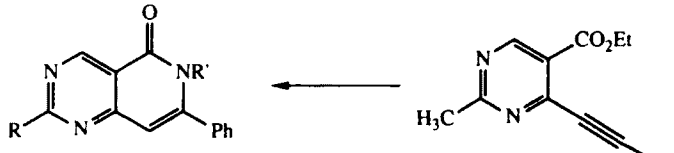
46 **47**

Another general approach involves an unsaturated carbon at position 6. Wibberley and his co-worker[26] reported a novel method in which pyrano[4,3-

d]pyrimidin-5-ones, **49**, are formed by the bromination of 4-styrylpyrimidine-5-carboxylic acids, **48**. These lactones give pyrido[4,3-*d*]-pyrimidin-5-ones, **50** (R = Ph; R′ = H, OH, or NH_2), on treatment with ammonia, hydroxylamine, or hydrazine.



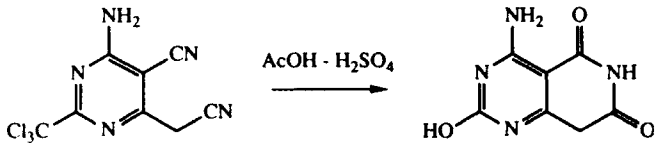
48 **49**



50 **51**

An alternate route is available through the palladium-catalyzed cross-coupling of phenylacetylene with 4-chloro-5-(ethoxycarbonyl)-3-methylpyrimidine to produce the alkyne, **51**. Subsequent cyclization with ethanolic ammonia gives the pyrido[4,3-*d*]pyrimidine ring system, **50** (R = Me; R′ = H).[28] Although not explored further, it seems reasonable other substituents on either the pyridine ring or on the pendant phenyl ring would lead to a larger array of derivatives.

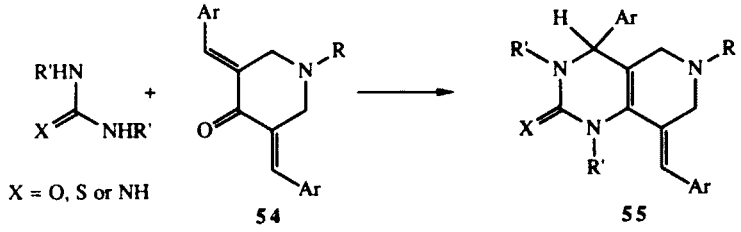
The remaining example was discovered as part of an overall study of the chemistry of *o*-aminonitriles and has not been explored further. Thus, treatment of 4-amino-2-trichloromethyl-5-cyano-6-cyanomethylpyrimidine, **52**, with sulfuric acid leads to the cyclized pyrido[4,3-*d*]pyrimidine, **53**, in excellent yield.[29]



52 **53**

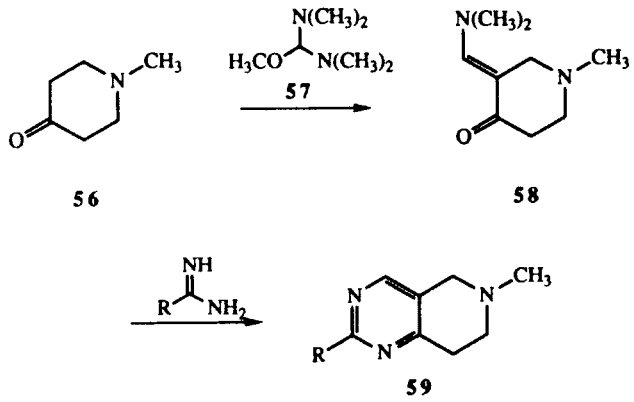
(2) *From Pyridines*

Pyrido[4,3-*d*]pyrimidines, in various oxidation states, have been obtained by cyclization of the pyrimidine ring onto an already existent pyridine nucleus. Cyclic α,β-unsaturated ketones, for example, have served as substrates for this type of fusion. The synthesis of 2-oxo, 2-thioxo, and 2-imino pyrido[4,3-*d*]pyrimidines, **55**, from 3,5-diarylidene-1-alkyl-4-piperidones, **54**, by condensation with ureas and thioureas[30] or guanidine[31] is illustrative of this method.



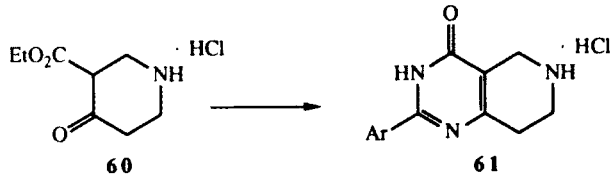
54 55

The use of simpler piperidones leads also to less substituted products. Bennett et al.[32] described a synthesis of several fused pyrimidines. By this method, treatment of 1-methyl-4-piperidone, **56**, with Bredereck's reagent, **57**,[33] gave the enamine **58**, which, following cyclization with an amidine equivalent, gave the reduced pyrido[4,3-*d*]pyrimidines, **59**. This amidine cyclization was found to be most successful when one equivalent of sodium ethoxide was used rather than under neutral or acidic conditions.



56 58 59

In a similar fashion, the condensation of arylamidines with the cyclic β-keto ester, 3-(ethoxycarbonyl)-1-methyl-4-piperidone, **60**, leads to the 5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine ring system, **61**.[37] Elslager et al.[38] reported the synthesis of several 2,4-diaminopyrido[4,3-*d*]pyrimidines, analogous to **59**, via condensation of cyclic enaminonitriles with guanidine.



60 61

4-Aminopiperidines also serve as suitable precursors to this fused pyrimidine ring. Kretzschmar and Dietz[34] reported a synthesis of decahydropyrido[4,3-*d*]pyrimidines, **65** and **66**, by the reaction of 1-benzyl-4-amino-3-aminomethyl