Synthesis of 4-Mono and 2,4-Disubstituted Pyrido [4,3-d] pyrimidines

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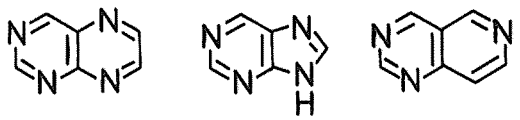
Introduction

Until recently, a number of pyridopyrimidines have been developed as folic acid antagonists(pteridine derivatives) and found that some of them have significant activity against microorganism.[1),2)] On the other hand, pyridopyrimidines including pyrido[2,3-d], pyrido [3,2-d], pyrido[3,4-d] and pyrido[4,3-d]pyrimidines



Pteridine Purine Pyrido[4,3-d]-pyrimidine

are deaza analogs of purine in which the imidazole of the latter is expanded to 6-membered ring. Because of the close structural similarity to purine, the deaza analogs might be anticipated to have similar biological activity. In fact, 2,4-disubstituted pyrido[2,3-d]pyrimidines have been shown to have anticytokinin activity.[3)] **However, systematic study of those four pyridopyrimidines as cytokinins has not appeared as yet. Since the study is regarded as an alternative approach of deazapurines,[4),5),6),7)] it is therefore worth while studying in order to specify nitrogen atom(s) relevant to substrate-receptor binding. In addition, there have been few studies on simple mono and di-substituted analogs, whereas highly substituted pyridopyrimidines have been well studied. In a series of our systematic study of pyridopyrimidines, synthesis of some 4- and 2,4-disubstituted pyrido[4,3-d]pyrimidines was intended, where reaction conditions of chlorodehydroxylation[10),11)] and amination[12)] were reinvestigated in some details. Additionally, cytokinin activity of newly prepared compounds was studied in lettuce seed germination[13)] and betacyanin biosynthesis of *Amaranthus*.[14)]

Results and Discussion

Usually pyridopyrimidin-4(3H)-ones are converted to the corresponding 4-chloro compounds by treatment with $POCl_3$ in the presence or the absence of base.[15),16)] Among the compounds, 4-chloropyrido [4,3-d]pyrimidine(**2a**) is the most reactive for nucleophilic substitution[17)] and difficulty is accompanied in the synthesis due to serious degradation with moisture. It is rather curious to find that although chlorodehydroxylation of pyrido[4,3-d]pyrimidin-4(3H)-one(**1a**) was made in low yields, reports on further improvement of the reaction have not appeared. Therefore, chlorodehydroxylation with $POCl_3$ together with appropriate base, *N,N*-dimethylaniline or triethylamine, was studied in some more details. In order to avoid degradation during work-up care was taken of minimum contact with moisture by rapid chromatographic separation of the reaction mixture instead of the method of Scarborough et al.[11)] Amounts of $POCl_3$ and base added were varied and the yields of the chloride(**2a**) were determined as isolated. As coarsely inspected(Table 1), it is

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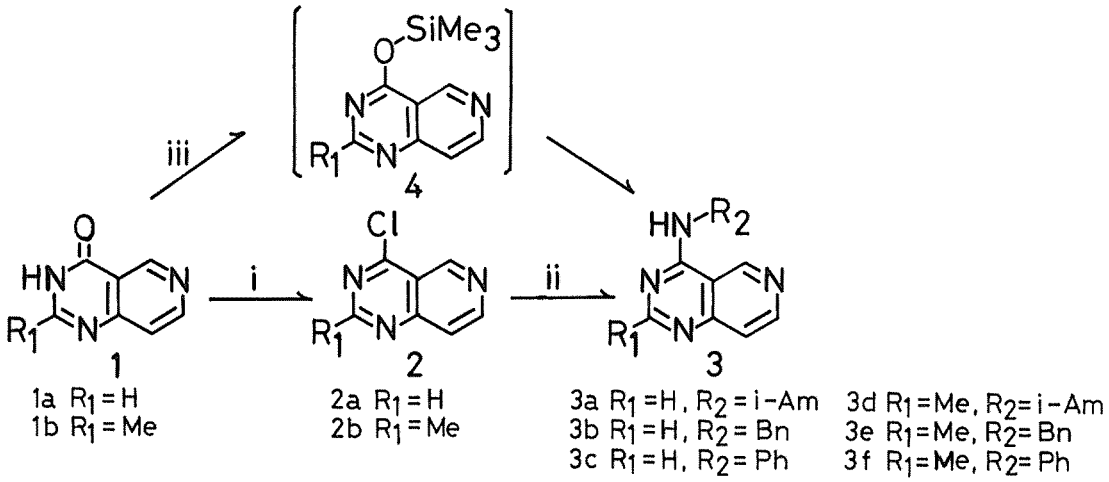
** Other polyazaaromatic compounds also exhibit cytokinin activity, although the activity is weak.[8),9)]



i) $POCl_3$, Et_3N or $PhNMe_2$ / Benzene ; ii) R_2NH_2 / EtOH;
iii) R_2NH_2, $(NH_4)_2SO_4$ / HMDS

Table 1. Chlorodehydroxylation of Pyrido[4,3-d]pyrimidin-4(3H)-one(**1a**)

run	base	amount of base, eq.	amount of $POCl_3$, eq.	yield, %
1	*N,N*-dimethylaniline	2	2/3	0
2	"	9	2/3	0
3	"	6	2	18
4	"	7.5	2.5	22
5	"	9	3	45
6	"	2	3	trace
7	triethylamine	2	2/3	20
8	"	6	2	50
9	"	7.5	2.5	50
10	"	9	3	56

pyrido[4,3-d]pyrimidin-4(3H)-one; 1.0 mmole, refluxed in benzene for 5 hr.

found that when *N,N*-dimethylaniline is used as base the yields of 2a increase as more $POCl_3$ is added(run 3 to 5) and that the use of less amount of $POCl_3$ and excess of *N,N*-dimethylaniline and vice versa decreases the yields or completely inhibits the reaction(run 2 and run 6). ***Therefore, it seems essential for effective chlorodehydroxylation of **1a** that amounts of the two reagents should be increased at the same time. When triethylamine was used in place of *N,N*-dimethylaniline, similar tendency was observed except that the chloride(**2a**) was obtained in 20% yield when 2/3 eq. of $POCl_3$ and 2 eq. of the base were added(run 7). The chloride(**2a**) was obtained in 56% yield when 3 eq. of $POCl_3$ and 9 eq. of trietylamine were used, the yield being higher than in any cases of *N,N*-dimethylaniline. From these results it is concluded that triethylamine is superior to *N,N*-dimethylaniline as base for the chlorodehydroxylation of the 4(3H)one (**1a**).

The similar reaction was applied to the 2-methyl analog(**1b**). When *N,N*-dimethylaniline was used, even

*** Small amounts of both $POCl_3$ and the base, the ratio of which was 1:3 as reported,[11] did not give 2a(run 1).

Table 2. Chlorodehydroxylation of 3-Methylpyrido[4,3-d]pyrimidin-4(3H)-one(**1b**)

run	base	amount of base, eq.	amount of $POCl_3$, eq.	yield, %
1	triethylamine	2	2/3	19
2	"	9	2/3	20
3	"	6	2	3
4	"	7.5	2.5	0
5	"	9	3	0

2-methylpyrido[4,3-d]pyrimidin-4(3H)-one; 1.0 mmole, refluxed in benzene for 5 hr.

a trace of the corresponding chloride (**2a**) was not formed under any conditions investigated. In contrast, the reaction in the presence of triethylamine gave **2b** in ca. 20% yields (run 1 and 2 in Table 2), although the yields were very low. Addition of large excess of both $POCl_3$ and triethylamine compared to **1b** decreased the yields markedly or completely(run 3,4 and 5 in Table 2). Chlorodehydroxylation of **1b** is more difficult than its counterpart(**1a**), probably due to more higher reactivity of **2b** than **2a**. Since the 4-chloro compounds, (**2a**) and (**2b**), were very sensitive to moisture, freshly prepared samples were used immediately for subsequent amination.

Table 3. Synthesis of 4-Substituted-aminopyrido[4,3-d]pyrimidines(3)

amine	product		mp., °C	yield, %	
	R1	R2		a*	b**
$BnNH_2$	H	Bn	180-182	83	77
i-$AmNH_2$	H	i-Am	158-159	77	68
$PhNH_2$	H	Ph	255-258	68	#
$BnNH_2$	Me	Bn	172-174	81	84
i-$AmNH_2$	Me	i-Am	155-159	70	52
$PhNH_2$	Me	Ph	240-244	76	#

*; reaction of 4-chlorides, **2a** and **2b**, with amine.

; reaction of 4(3H)-ones, **1a and **1b**, with amine in HMDS in the presence of ammonium sulfate.

#; The corresponding 4-amino derivative was obtained as a major product.

Amination of **2a** and **2b** was achieved in ethanol at room temperature in a few minutes in good yields irrespective of nucleophilicity of amines used(Table 3). As the chlorides are highly reactive, even less nucleophilic aniline reacts with those to give the corresponding 4-substituted compound, (**3c**) and (**3f**), in high yields under mild conditions as expected. Therefore, overall yields of **3a** to **3f** from the 4(3H)ones, (**1a**) and (**1b**), seriously depend on effectiveness of chlorodehydroxylation.

To avoid ineffective chlorodehydroxylation, an alternative one-pot amination of **1a** and **1b** with amines in hexatrimethylsilyl disilazan(HMDS)[18] was attempted. In the reaction 4-trimethylsilyloxyl derivatives(**4**), which are generated *in situ*, are less reactive intermediates than the corresponding chlorides(**2**) and require elevated temperature for smooth reaction with amines.[18] The reaction with more nucleophilic iso-amylamine and benzylamine gave the desired aminated products in 52-84% yields, whereas the reaction with less nucleophilic aniline failed. In the latter case, 4-aminopyrido[4,3-d]pyrimidine and 2-methyl-4-aminopyrido[4,3-d]pyrimidine were obtained as main products respectively, the structure of which were supposed from their IR and ^1H NMR data. Elevation of reaction temperature to 140°C in a sealed tube and use of bis(trimethylsilyl) acetamide as silylating agent gave only a detectable amount of the product(**3f**).

From above results, amination of pyrido[4,3-d]pyrimidin-4(3H)-ones, (**1a**) and (**1b**), with amines in HMDS

is not suitable for less nucleophilic amine. However, the method is very effective for amination of the compounds with more nucleophilic amine and provides a convenient route to 4-substituted aminopyrido[4,3-d]pyrimidines in high yields.

In this study, it was found that the yield of 4-chloro compound (**2a**) could be improved to 56% by changing amounts of $POCl_3$ and base added, the yield being higher than ever reported. However, similar chlorodehydroxylation of **1b** was not satisfactory in spite of our efforts, probably due to instability of the chloride(**2b**).

Cytokinin activity of 4- and 2,4-disubstituted pyrido[4,3-d]pyripyrimidines, (**3a**) to (**3f**), were tested in promotion of lettuce seed germination and betacyanin biosyntheses of *Amaranthus*. All of those compounds showed no cytokinin activity in the tests practically, suggesting that position of nitrogen atom in the pyridopyrimidine ring is important for effective substrate-receptor binding. Although potential cytokinins were not found in a series of 4-substituted aminopyrido[4,3-d]pyrimidines, efforts to synthesize remaining pyridopyrimidine analogs have been continued to search for new cytokinins.

Experimentals

General Methods

Melting points were measured with a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were measured with a JUSCO IR-G spectrometer. ^1H NMR spectra were recorded on Hitachi R-22 spectrometer at 90 MHz and expressed in parts per million down-field shift from Me_4Si. UV spectra were determined with a Hitachi UV 200-10 spectrophotometer and mass spectra(electron impact) were obatined with a Hitachi M-50 spectrometer at 70 eV. For thin layer chromatography(TLC) and column chromatography, Wako gel B-5 and B-10(3:5 mixture) and Wako gel C-200(Wako Pure Chemicals Co.) were used respectively. Elemental analyses were performed by the Analytical Center, Kyoto University, Kyoto.

Benzene was distilled and dried over sodium wire. Other commercially available reagents were simply distilled before use or used without further purification.

Bioassay

Germination test was done by using lettuce seed Great Lakes 366 according to the method of Skinner et al.[13] Promotion of betacyanin biosynthesis of *Amaranthus* was tested by the method of Biddington et al.[14] with a slight modification. Experimental details of these bioassay methods for quantitative structure-activity study will be published elsewhere.

Pyrido[4,3-d] pyrimidin-4(3H) -one (**1a**)

The title compound, mp, 305-308°C(Lit. 308-310°C)[19] was prepared from 3-picoline via 4-aminonicotinic acid in 6 steps in 6.4% overall yield according to the reported method.[19] Spectral data of all intermediates were in accordance with their assigned structures.

2-Methylpyrido[4,3-d] pyrimidin-4(3H) -one (**1b**)

The 4(3H)one, mp. 316-320°C(Lit. 308-310°C)[20] was synthesized in 66% yield from 4-aminonicotinic acid via 2-methylpyrido[4,3-d]-1,3-oxazin-4-one according to the reported method.[20]

4-Chloropyrido[4,3-d] pyrimidine (**2a**)

The chloride was synthesized according to the method of Scarborough et al.[11] with a slight modification with respect to isolation procedures.

To a suspension of finely pulverized **1a** (148 mg, 1.0 mmole) in anhydrous benzene(30 ml) were added $POCl_3$(0.27 ml, 3.0 mmole) and triethylamine(1.27 ml, 9.0 mmole) and the mixture was refluxed with stirring for 5 hr. After removal of dark solid by filtration, the orange-yellow filtrate was immediately submitted to short silica gel column chromatography. Successive elutions with benzene and benzene-ethyl acetate(2:1) gave **2a** (105 mg, 56%), mp. 80-85°C(Lit. 82-83°C)[10] as colorless crystals on evaporation of the solvents under

reduced pressure. IR(KBr)1600(aromatic), 700(C-Cl) cm^{-1}; UV:λ_{max}^{EtOH} 266(ε 3,540), $\lambda_{max}^{EtOH,pH1}$310(ε 2,020), 270(ε 8,130) nm; ^1H NMR($CDCl_3$)7.91(1H, dd, J=0.8 Hz, and 6.0 Hz, 8-H), 9.03(1H, d, J=6.0 Hz, 7-H), 9.21(1H, s, 2-H), 9,72(1H, d, J=0.8 Hz, 5-H).

For revision of reaction conditions the ratio of $POCl_3$ to base, triethylamine or *N,N*-dimethylaniline, was varied.

2-Methyl-4-chloropyrido [4,3-d] pyrimidine (**2b**)

The chloride was prepared from **1b** analogously. Chromatographic separation on silica gel gave the pure **2b**, mp. 99-101°C, in 19% yield, which became yellow on storage. IR(KBr)1600(aromatic), 660(C-Cl) cm^{-1}; UV:λ_{max}^{EtOH} 265(ε 2,960), $\lambda_{max}^{EtOH,pH1}$274(ε 10,200), 241(ε 3,800) nm; ^1H NMR($CDCl_3$)2.88(3H, s, $-CH_3$), 7.81(1H, dd, J=0.8 Hz and 6.0 Hz, 8-H), 8.96(1H, d, J=6.0 Hz, 7-H), 9.60(1H, d, J=0.8 Hz, 5-H).

Reaction of the chloride (**2**) *with amines* (*method a*)

Typical procedures are as follows. To a solution of **2**(1.0 mmole) in ethanol(20 ml) was added amine(3.0 mmole) dissolved in a small amount of the solvent and the mixture was stirred for a few minutes at room temperature. After the completion of the reaction was detected by TLC, the solvent was removed under reduced pressure and the crystalline residue was purified by further crystallization from water.

Reaction of the 4(3H) one (**1**) *with amines* (*method b*)

Substitution of 4-trimethylsilyloxyl derivative(**4**) of **1** with amines was made according to the method of Vorbrüggen et al.[18] A mixture of **1**(1.0 mmole), hexamethyldisilazan(3.0 mmole), amine(3.0 mmole), and ammonium sulfate(0.1 mmole) was refluxed until the mixture became clear. Then, to the solution was added ethanol(10 ml) and evaporated to give the residue, which was crystallized from water.

4-iso-Amylaminopyrido [4,3-d] pyrimidine (**3a**)

Method a and b gave **3a**, mp. 158-159°C, in 77% and 68% yields, respectively. IR(KBr)3400, 3100(NH), 2900(aliphatic), 1600(aromatic) cm^{-1}; UV:λ_{max}^{pH1} 320(ε 9,500), 310(ε 9,250), 241(ε 13,400), λ_{max}^{pH7} 308(ε 12,700), 241(ε 14,800), λ_{max}^{pH13} 310(ε 11,600), 237(ε 11,000)nm; ^1H NMR(DMSO-d6)0.94(6H, d, J=6 Hz, $-CH_3$), 1.4-1.8(3H, m, $=CH-CH_2-$), 3.60(2H, m, $-N-CH_2-$), 7.56(1H dd, J=0.8 Hz and 6.0 Hz, 8-H), 8.62(1H, s, 2-H), 8.70(1H, broad s, NH), 8.72(1H, d, J=6.0 Hz, 7-H), 9.50(1H, d, J=0.8 Hz, 5-H); Mass:m/z(relative intensity)216(M^+, 26), 201(13), 174(71), 160(95), 147(100), 131(56), 120(33), 104(58), 76(65). Anal. Calcd for $C_{12}H_{16}N_4$: C, 66.64, H, 7.46; N, 25.91. Found: C, 66.84; H, 7.52; N, 25.61.

4-Benzylaminopyrido [4,3-d] pyrimidnine (**3b**)

Preparation by method a and b afforded **3b**, mp. 180-182°C, in 83% and 77% yields, respectively. IR(KBr)3400, 3100(NH),2900, 1600(aromatic) cm^{-1}; UV: λ_{max}^{pH1} 320(ε 9,500), 310(ε 9,250), 241(ε 13,400), λ_{max}^{pH7} 308(ε 12,700), 241(ε 14,800), λ_{max}^{pH13} 310(ε 11,600), 237(ε 11,600) nm; ^1H NMR(DMSO-d6)4,87(2H, d, J=6 Hz, $N-CH_2-$), 7.2-7.5(5H, aromatic), 7.60(1H, dd, J=0.8 Hz and 6.0 Hz, 8-H), 8.63(1H, s, 2-H), 8.76(1H, d, J=6.0 Hz, 7-H), 9.49(1H, t, J=6 Hz, NH), 9.80(1H, d, J=0.8 Hz, 5-H); Mass:m/z(relative intensity)236(M^+, 67), 149(16), 130(17), 106(100), 91(64), 77(49). Anal. Calcd for $C_{14}H_{14}N_4$: C, 71.17; H, 5.12; N, 23.72. Found: C, 71.13; H, 5.05; N, 23.47.

4-Phenylaminopyrido [4,3-d] pyrimidine (**3c**)

The title compound, mp. 255-258°C, was synthesized in 68% yield by method a. IR(KBr)3400, 3100(NH), 2900, 1600(aromatic) cm^{-1}; UV: λ_{max}^{pH1} 332(ε 8,400), 266(ε 8,000), 222(ε 15,700), λ_{max}^{pH7} 321(ε 10,900), 230(ε 12,400), λ_{max}^{pH12} 340(ε 10,100), 252(ε 11,900) nm; ^1H NMR(DMSO-d6) 7.1-8.0(5H, aromatic), 7.17(1H, dd, J=0.8 Hz and 6.0 Hz, 8-H), 8.47(1H, s, 2-H), 8.83(1H, d, J=6.0 Hz, 7-H), 9.91(1H, d, J=0.8 Hz, 5-H); Mass:m/z(relative intensity)222(M^+, 100), 206(9), 195(8), 168(9), 150(8), 131(9), 104(25), 92(22), 77(46), 76(46). Anal. Calcd for $C_{13}H_{10}N_4$: C, 70.26; H, 4.54; N, 25.21. Found: C, 70.18; H, 4.35; N, 24.99.

2-Methyl-4-iso-amylaminopyrido [4,3-d] pyrimidine (**3d**)

The title compound, mp. 155-159°C, was prepared in 70% yield by method a. The reaction by method b also gave the compound in 52% yield. IR(KBr)3450, 3250(NH), 3100, 1600(aromatic) cm^{-1}; UV: $\lambda_{max}^{pH\,1}$ 332(ε 6,400), 321(ε 6,700), 225(ε 7,800), $\lambda_{max}^{pH\,7}$ 332(ε 6,900), 321(ε 7,600), 255(ε 7,500), $\lambda_{max}^{pH\,13}$ 330(ε 5,300), 280(ε 7,500) nm; ^{1}H NMR(DMSO-d6)0.89(6H, d, J=6 Hz, $-CH_3$), 1.3-1.8(3H, m, $=CH-CH_2-$), 2.44(3H, s, $-CH_3$), 3.56(2H, m, $N-CH_2-$), 7.43(1H, dd, J=0.8 Hz, and 6.0 Hz, 8-H), 8.53(1H, broad, NH), 8.62(1H, d, J=6.0 Hz, 7-H), 9.38(1H, d, J=0.8 Hz, 5-H); Mass:m/z(relative intensity)230(M^+, 26), 215(14), 187(58), 174(70), 160(100), 144(86), 119(25), 103(63), 76(58). Anal. Calcd for $C_{13}H_{18}N_4$: C, 67.79; H, 7.88; N, 24.33. Found: C, 67.86; H, 8.00; N, 24.37.

2-Methyl-4-benzylaminopyrido [4,3-d] pyrimidine (**3e**)

The title compound, mp. 172-174°C, was prepared by method a and b in 81% and 84% yields respectively. IR(KBr)3300, 3250(NH), 3100, 1600(aromatic) cm^{-1}; UV: $\lambda_{max}^{pH\,1}$ 320(ε 12,900), 310^{sh}(ε 11,900), 328(ε 17,500), $\lambda_{max}^{pH\,7}$ 307(ε 14,500), 235(ε 14,800), $\lambda_{max}^{pH\,13}$ 308(ε 14,500), 235(ε 14,800) nm; ^{1}H NMR(DMSO-d6)2.46(3H, s, $-CH_3$), 4,87(2H, d, J=6 Hz, $N-CH_2-$), 7.2-7.5(5H, aromatic), 7.52(1H, dd, J=0.8 Hz and 6.0 Hz, 8-H), 8.72(1H, d, J=6.0 Hz, 7-H), 9.22(1H, d, J=0.8 Hz, 5-H); Mass:m/z(relative intensity)250(M^+, 80), 235(8), 208(7), 180(8), 173(8), 144(31), 103(100), 90(63), 76(45), 75(44). Anal. Calcd for $C_{15}H_{14}N_4.1.75H_2O$: C, 63.93; H, 6.26; N, 19.88. Found: C, 63.98; H, 6.17; N, 20.00.

2-Methyl-4-phenylaminopyrido [4,3-d] pyrimidine (**3f**)

The pyridopyrimidine, mp. 240-244°C, was prepared in 76% yield by method a. IR(KBr)3600-2900(NH and aromatic), 1600(aromatic) cm^{-1}; UV: $\lambda_{max}^{pH\,1}$ 332(ε 12,300), 233(ε 17,400), $\lambda_{max}^{pH\,7}$ 325(ε 12,700), 232(ε 15,700), $\lambda_{max}^{pH\,12}$ 332(ε 12,900), 252(ε 12,700) nm; ^{1}H NMR(DMSO-d6) 2.51(3H, s, $-CH_3$), 7.1-8.0(5H, aromatic), 7.57(1H, broad d, 8-H), 8.78(1H, broad s, 5-H); Mass:m/z(relative intensity)236(M^+, 100), 221(11), 194(18), 168(15), 149(12), 144(22), 118(14), 103(43), 76(51). Anal. Calcd for $C_{14}H_{12}N_4$: C, 71.17; H, 5.12; N, 23.29. Found: C, 70.97; H, 5.13; N, 23.29. Extremely broad signals of 5-H, 7-H and 8-H protons were observed in ^{1}H NMR.

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摘　　要

4-置換及び2,4-二置換ピリド〔4,3-d〕ピリミジン類の合成

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ピリドピリミジン類の系統的な合成とサイトカイニン活性に関する研究の一環として，4-置換及び2,4-二置換ピリド〔4,3-d〕ピリミジン類の合成を行なった。多置換化合物の合成研究に比べ，一置換物及び二置換物のような簡単な化合物については合成中間体の不安定さのために十分な研究がなされていなかった。そこで4位にアミノ基を導入するために塩素置換反応及びアミノ化反応を詳しく検討した。その結果，塩素置換反応に用いる塩基触媒としてはN,N-ジメチルアニリンよりトリエチルアミンの方が優れており，ピリド〔4,3-d〕ピリミジン-4(3H)-オンに対するオキシ塩化リンと塩基の比を変えることにより最高56%の収率で4-クロル体を合成することができることが判った。一方2-メチルピリド〔4,3-d〕ピリミジン-4(3H)-オンの塩素化においては生成する4-クロル誘導体の不安定さのために低収率でしか得られなかった。4-クロル体のアミノ化反応においては求核性の高い脂肪族アミンと同様に求核性の低い芳香族アミンも温和な条件下約70～80%の好収率で目的物を与えた。また不安定な4-クロル体を経由しない，4(3H)オンのヘキサトリメチルジシラザン，硫酸アンモニウム及びアミンとのアミノ化反応についても検討した。芳香族アミンは目的物を与えなかったが，脂肪族アミンは4-クロル体のアミノ化反応と同様の好収率で目的物を与え，簡便な4-置換アミノピリド〔4,3-d〕ピリミジン類の合成法であることが判った。

合成した化合物のサイトカイニン活性をレタス発芽テスト及びひもげいとうによるベタシアニン色素形成テストにより調べたが，いづれも不活性であった。