PYRIMIDINE N-OXIDES: SYNTHESES, STRUCTURES, AND CHEMICAL PROPERTIES

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Abstract——The syntheses and reactions of pyrimidine N-oxides are reviewed. Pyrimidines having alkyl, aryl, and alkoxyl groups are convertible to their mono-N-oxides by N-oxidation with an organic peroxy acid. The position of the N-oxide group can be elucidated by physical methods. Pyrimidine N-oxides are highly reactive to various nucleophilic reagents owing to their π-deficient character. The reactivity of a methyl group enhanced by introducing an N-oxide group and the characteristic ring-cleavage of N-oxides are also described.

CONTENTS

I. INTRODUCTION

In connection with studies of pyridine and quinoline N-oxides[1,2] Ochiai *et al.* examined the N-oxidation of N-heteroaromtics other than pyridine and quinoline, and in 1945, they repoted that 4-methylpyrimidine was converted into a mono-N-oxide by treatment with monoperphthalic acid.[3] This was the beginning of pyrimidine N-oxide chemistry.

Since then, the chemistry of pyrimidine N-oxides has been progressing slowly but steadily. Compared with the chemistry of pyridine and quinoline N-oxides, that of pyrimidine N-oxides is less developed, probably due to the following reasons.

(1) Pyrimidine N-oxides are less stable under strongly acidic conditions, so that vigorous electrophilic reactions such as nitration and sulfonation usually

result in decomposition of the substrates.

(2) A satisfactory variety of ring-closure reactions have been developed for the synthesis of pyrimidine derivatives. Hence it is seldom necessary to use N-oxide chemistry when a specific pyrimidine derivative is required.

In spite of this situation, much progress has been made in the synthesis of pyrimidine N-oxides, with consequent clarification of their unique properties. In this review, we summarize the syntheses and reactions of pyrimidine N-oxides.

II. SYNTHESES OF PYRIMIDINE N-OXIDES BY N-OXIDATION

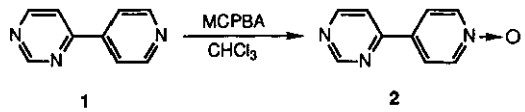
A. General Aspects (Reagents and Reaction Conditions)

Hydrogen peroxide (H_2O_2) in acetic acid, which is one of the most popular reagents for N-oxidation of pyridine and quinoline derivatives, is not recommended automatically for the N-oxidation of pyrimidine derivatives, except in the case of 4,6-di- or 2,4,6-trisubstituted derivatives. Under these conditions, unfavorable side-reactions, such as oxidation of the ring or its substituents or the hydrolysis of substituents, may spoil N-oxide formation (see Section II,F).

On the other hand, oxidation with organic peroxy acids such as m-chloroperbenzoic acid (MCPBA) and monoperphthalic acid can be used with confidence. Maleic anhydride with H_2O_2 in chloroform is also recommended as an oxidative reagent, in which monopermaleic acid is the active constituent. In the N-oxidation of various aminopyrimidines, H_2O_2 in trifluoroacetic acid has been used as an efficient reagent.[4-9]

The reaction of 4-(4-pyridyl)pyrimidine (1) with MCPBA resulted in the selective formation of 4-(4-pyrimidinyl)pyridine 1-oxide (2).[10] This result indicates that pyrimidine is less reactive than pyridine towards N-oxidation, probably owing to the lower basicity of the ring nitrogen atoms in the former (pyridine: pKa=5.23, pyrimidine: pKa=1.34).

Treatment of 2,4,6-trimethylpyrimidine with excess H_2O_2 in acetic acid gave the mono-N-oxide as the sole product,[11] whereas the reaction of 2,3,5,6-tetramethylpyrazine with 4 molar equivalents of H_2O_2 under similar conditions afforded the di-N-oxide.[12] This is a typical example of the resistance of the pyrimidine ring towards di-N-oxide formation. As evident from the following sections, there are no paper dealing with the di-N-oxidation of pyrimidines other than diamino- and triaminopyrimidines.

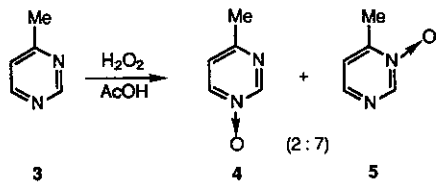


1 2

Scheme 1

B. N-Oxidation of Alkylpyrimidines

Alkylpyrimidines are usually oxidized to their mono-N-oxides, and no data have been reported on the formation of alkylpyrimidine di-N-oxides by N-oxidation. When 4-methylpyrimidine (3) was heated with H_2O_2 in acetic acid at 60-70°C, a mixture of 4-methylpyrimidine 1-oxide (4) and the 3-oxide (5) was formed in a ratio of 2:7.[13] Moreover, the N-oxidation of 2,4-dimethylpyrimidine with MCPBA afforded a mixture of the 1-oxide (35%) and the 3-oxide (32%).[14,15] As indicated by these results, the N-oxidation of unsymmetrical alkylpyrimidines affords a mixture of the 1-oxide and the 3-oxide. The isolated yield of each isomer obtained by the N-oxidation of some unsymmetrically substituted 2,4,6-trialkylpyrimidines is listed in Table I.[16,17]



3 4 5

Scheme 2

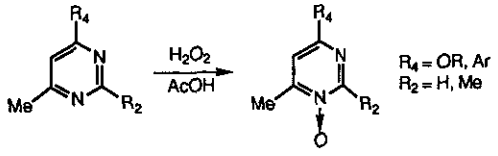
Table I. N-Oxidation of Unsymmetrically Substituted Pyrimidines with H_2O_2 in Acetic Acid

Substituent			Yield(%)	
2-	4-	6-	1-Oxide	3-Oxide
Me	Et	Me	30	25
^{i}Pr	Et	Me	28	18
Ph	Et	Me	22	12
Me	CH_2Ph	Me	18	15
Me	Ph	Me	40	0.6

Based on the results listed above, it is clear that the N-oxidation of 4-alkyl- and 2,4-dialkylpyrimidines has little value as a synthetic procedure. On the other hand, the reaction of 4,6-dialkylpyrimidines, in which the alkyl groups are identical, is synthetically advantageous in yield and purity of product. For example, the N-oxidation of 4,6-dimethylpyrimidine gave the 1-oxide in good yield.[18-21]

C. N-Oxidation of Alkoxy- and Arylpyrimidines

The reactions of 4-methoxy-2,6-dimethyl- and 4-methoxy-6-methylpyrimidine with H_2O_2 in acetic acid gave the corresponding 4-methoxypyrimidine 1-oxides as sole products.[21-24] Similarly, 2,4-dimethyl-6-phenyl- and 4-methyl-6-phenylpyrimidine were oxidized to their 3-oxides.[17-19,22] Based on these findings, it is evident that alkoxyl and phenyl groups retard the oxidation at the adjacent nitrogen atom, while oxidation at the nitrogen atom remote from these substituents is rather favored. The reason is not clear at present, but it is well known that 4-methoxypyrimidine (pKa=2.5) has a higher basicity than pyrimidine itself, and conversely 2-methoxypyrimidine (pKa<1.0) has a lower basicity than pyrimidine.



Scheme 3

The N-oxidation of 4-methoxypyrimidine[14,21,25] and 4-phenylpyrimidine[14,22,26] also afforded the corresponding 1-oxides, although the yield of each N-oxide was decreased by some oxidative ring-cleavage as described in Section I,F,3.

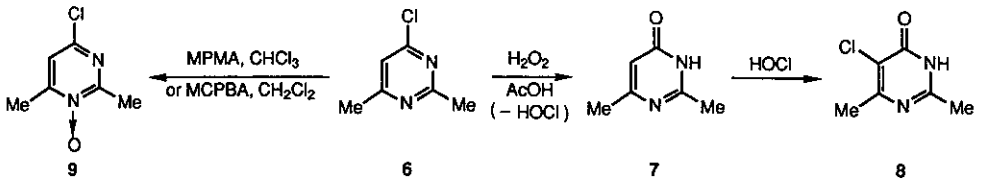
Additionally, it should be mentioned that the N-oxidation of 4-phenoxypyrimidines is better carried out with an organic peroxy acid in an aprotic solvent,[24] because the 4-phenoxyl group is so susceptible to hydrolysis that H_2O_2 in acetic acid causes cleavage of the ether bond prior to N-oxidation.[27] N-Methyl-4-pyrimidinones are completely resistant to N-oxidation although appreciably basic nitrogen atoms remain in the substrates.[28]

D. N-Oxidation of Halopyrimidines

5-Halopyrimidines are convertible into their mono-N-oxides. For example, the reaction of 5-bromopyrimidine with H_2O_2-sodium tungstate[29] or MCPBA[30,31] gave the 1-oxide in comparable yield.

On the other hand, a unique chlorination of the pyrimidine ring has been reported during one attempted N-oxidation of a 4-chloropyrimidine. When 4-chloro-2,6-dimethylpyrimidine (**6**) was heated with H_2O_2 in acetic acid, 5-chloro-2,6-dimethyl-4(3H)-pyrimidinone (**8**) resulted instead of 4-chloro-2,6-dimethylpyrimidine 1-oxide (**9**).[32] In contrast, **9** was prepared successfully by treatment of **6** with H_2O_2-maleic anhydride,[32] or MCPBA,[33] without concomitant formation of the 3-oxide. The pathway from **6** to **8** is assumed to involve hydrolysis of **6** followed by an electrophilic

chlorination of **7** as illustrated in Scheme 4. Another such chlorination has been observed during the reaction of 1-chloroisoquinoline with H_2O_2 in acetic acid.[34]



9 **6** **7** **8**

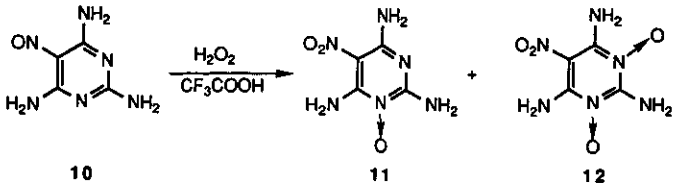
Scheme 4

E. N-Oxidation of Aminopyrimidines

The N-oxidation of 2-aminopyrimidine with MCPBA in acetone afforded 2-aminopyrimidine 1-oxide in satisfactory yield,[35] while the N-oxidation of 4-aminopyrimidine and 4-alkylamino(or 4-dialkylamino)pyrimidines with the same reagent in acetonitrile afforded the corresponding 1-oxides in poor yields.[21] It is of interest that the amino groups exhibit a reverse substituent effect to that of the methoxyl group for pyrimidine N-oxide formation. Thus, 4-amino and 2-methoxyl groups retard the N-oxidation, whereas 2-amino and 4-methoxyl groups facilitate the reaction.

The N-oxidation of 2,4-diaminopyrimidine with MCPBA[36] gave a mixture of the 1- and 3-oxide, but the N-oxidation with H_2O_2 in trifluoroacetic acid[8] afforded only the 3-oxide. The N-oxidation of 2,4-diamino-6-chloropyrimidine with H_2O_2 in trifluoroacetic acid yielded the 3-oxide as the sole product.[5] Judging from these results, the predominant formation of 3-oxides from 2,4-diaminopyrimidines seems to be general.

It should be emphasized that the N-oxidation of 2,4-diamino-5-chloro-6-methylpyrimidine with H_2O_2 in trifluoroacetic acid gave the di-N-oxide,[6] and the reaction of 2,4,6-triamino-5-nitrosopyrimidine (**10**) with the same reagent yielded the corresponding nitro mono- (**11**) and nitro di-N-oxide (**12**).[4] The ready formation of the polyaminopyrimidine di-N-oxides has been explained by the electron-donating character of amino groups, but we refrain from any further comment in view of the resistance of 4-aminopyrimidines towards N-oxidation with H_2O_2 in acetic acid, a fact confirmed in our laboratory.[28] In the above cases, powerful reaction conditions (H_2O_2 in trifluoroactic acid) were employed, but there are no data on the N-oxidation of alkyl-, aryl-, and alkoxypyrimidines under such conditions.



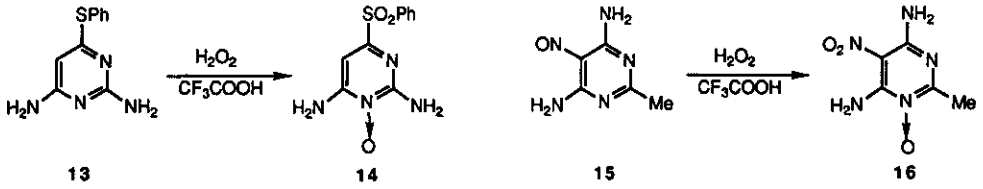
10 11 12

Scheme 5

F. Side Reactions

1. Oxidation of Substituents

Alkyl(or aryl)thio groups on pyrimidine rings, like those on pyridine rings, are oxidized to sulfonyl or sulfinyl groups,[33,37] in advance of N-oxide formation. Sulfonyl groups at the 2- or 4-position of pyrimidine rings generally disturb the N-oxidation by their electron-withdrawing effect, except in special cases such as 2,4-diamino-6-phenylthiopyrimidine (**13**).[6] The conversion of a nitroso group into a nitro group has been also observed during the N-oxidation of 5-nitrosopyrimidine derivatives (e.g. **15**).[4,6,7]



13 14 15 16

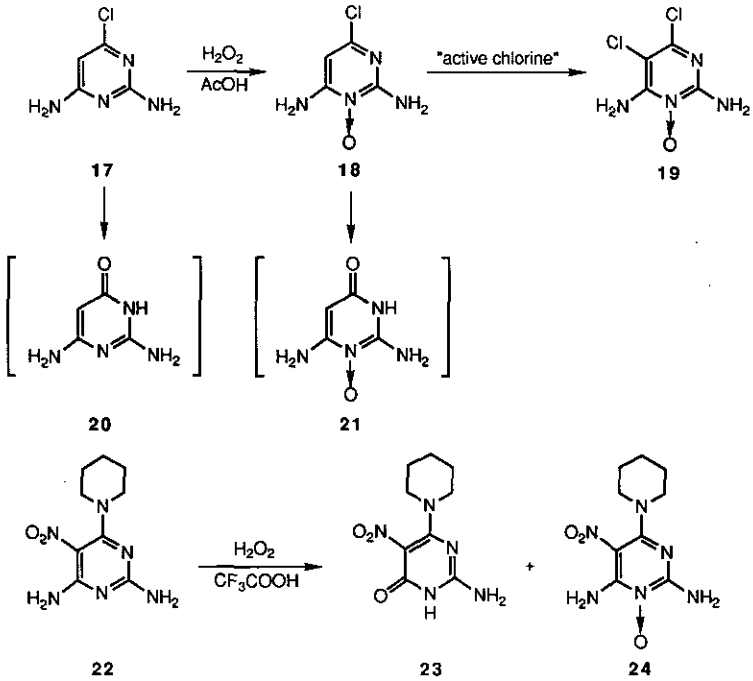
Scheme 6

The oxidation of carbon substitents such as hydroxymethyl, active methylene, or formyl groups has been frequently observed during the N-oxidation of pyridine and quinoline derivatives, but there is no report dealing with the N-oxidation of pyrimidine derivatives bearing such substituents.

2. Hydrolysis of Substituents

As described in Sections II,C and II,D, 4-chloro- and 4-phenoxypyrimidines are hydrolyzed with H_2O_2 in acetic acid. When 2,6-diamino-4-chloropyrimidine (**17**) was treated with 90% H_2O_2 in acetic acid, concomitant formation of 2,6-diamino-4,5-dichloropyrimidine 1-oxide (**19**) and 2,6-diamino-4-chloropyrimidine 1-oxide (**18**) was observed.[5] Although the hydrolysis products such as 2,6-diamino-4(3H)-pyrimidinone (**20**) and its 1-oxide (**21**), were not isolated, it has been reported that further chlorination of **18** with "active chlorine" generated from **18** afforded **19**.

In the case of 2,6-diamino-5-nitro-4-piperidinopyrimidine (**22**), conversion of the 6-amino group into a 6-hydroxyl group was observed during N-oxidation with H_2O_2 in trifluoroacetic acid.[6]



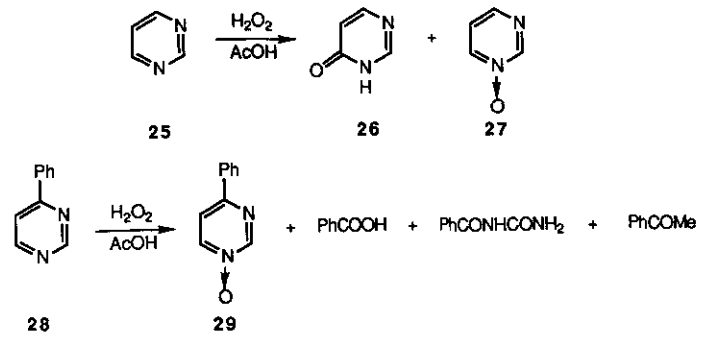
Scheme 7

The hydrolysis of cyano[38] and ethoxycarbonyl groups[39] has been reported for the N-oxidation of pyridine derivatives with H_2O_2 in acetic acid. These reactions are considered to occur in N-oxidation of corresponding pyrimidine derivatives, but there is no report dealing with N-oxidation of pyrimidine derivatives with such functional groups.

3. Oxidation of the Pyrimidine Ring

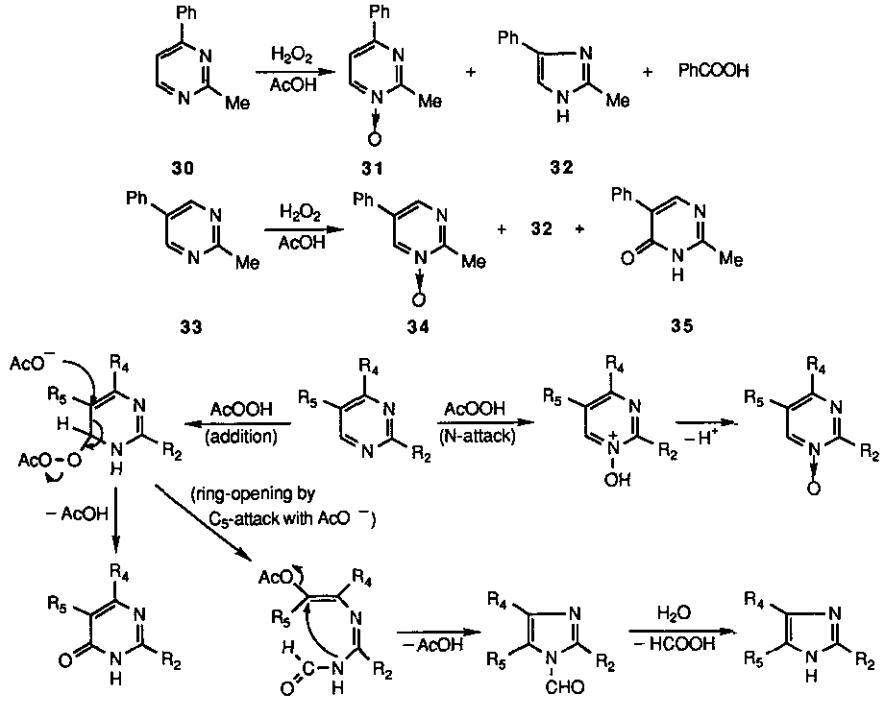
It is well known that the N-oxidation of quinazoline leads to 4(3H)-quinazolinone in quantitative yield.[40,41] Similarly, the N-oxidation of pyrimidine (**25**) has been reported to give 4(3H)-pyrimidinone (**26**) accompanied with a small amount of pyrimidine 1-oxide (**27**).[42]

The N-oxidation of 4-phenylpyrimidine (**28**) in H_2O_2-acetic acid has been reported to give considerable amounts of benzoic acid, benzoylurea, and acetophenone as well as 4-phenylpyrimidine 1-oxide (**29**).[22] The formation of benzoylurea provided evidence that cleavage of the pyrimidine ring could have started from an oxidation at the 6-position, although no 4-phenyl-6(1H)-pyrimidinone was isolated. Moreover, when 6-methyl-4-phenylpyrimidine was treated with the same reagent, the corresponding 1-oxide was isolated in satisfactory yield, along with a small amount of benzoic acid. This is further evidence of an attack at the 6-position.



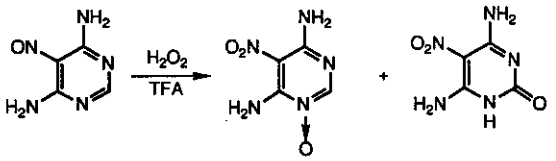
Scheme 8

In connection with such oxidation at the 4-position, a concomitant formation of 2-methyl-4-phenylimidazole (**32**) has been reported during the N-oxidation of 2-methyl-4-phenyl- (**30**) and 2-methyl-5-phenylpyrimidine (**33**).[14] A likely pathway to this by-product involves initiation by the nucleophilic addition of peracetic acid to the carbon-nitrogen double bond, as illustrated in Scheme 9.



Scheme 9

On the other hand, oxidation at the 2-position has been reported during the N-oxidation of 4,6-diamino-5-nitrosopyrimidine (**36**).[7] The strong electron-withdrawing effect of the nitro group, derived from the 5-nitroso group, may accelerate a nucleophilic addition of the peroxy acid to the carbon-nitrogen double bond between positions 1 and 2.



36 **37** **38**

Scheme 10

Table II summarizes all currently known results from the N-oxidation of pyrimidines, ignoring products other than N-oxides.

Table II. Yields of Pyrimidine N-Oxides by N-Oxidation

R_2	R_4	R_5	R_6	Method[a]	1-Oxide (%)	3-Oxide (%)	Reference
H	H	H	H	H_2O_2-AcOH	11		11
				H_2O_2-AcOH	6.5		42
				H_2O_2-AcOH	18-21		18,19
				H_2O_2-AcOH	9		20
				MCPBA-$CHCl_3$	48		14
				H_2O_2-Na_2WO_4	17		121
[2-Substituted Derivatives]							
Me	H	H	H	H_2O_2-AcOH	31		11
				MCPBA-$CHCl_3$	55		14
				MCPBA-MeCN	5		21
CH_2Ph	H	H	H	MCPBA-C_6H_6	88		100
Ph	H	H	H	MCPBA-$CHCl_3$	13		14
NH_2	H	H	H	MCPBA-acetone	56		35
				MCPBA-MeCN	40		21
NHMe	H	H	H	H_2O_2-AcOH	30		21
				MCPBA-MeCN	5		21
OMe	H	H	H	H_2O_2-AcOH	18		21
[4-Substituted Derivatives]							
H	Me	H	H	H_2O_2-AcOH	43		23
				H_2O_2-AcOH	31[b]		11
				H_2O_2-AcOH	28[b]		18,19
				H_2O_2-AcOH	—[c]		13
				MCPBA-$CHCl_3$	12	30	14
				MCPBA-MeCN	21	23	21
				MPPA-Et_2O	6.8[b]		3
H	CH_2Ph	H	H	MCPBA-C_6H_6	38	60	100
H	Ph	H	H	H_2O_2-AcOH	25	0	22
				H_2O_2-AcOH	24	0	14
				MCPBA-$CHCl_3$	64	0	14
				H_2O_2-Na_2WO_4	70	0	26
H	NH_2	H	H	MCPBA-MeCN	25	trace	21
H	NHMe	H	H	H_2O_2-AcOH	11	0	21
				MCPBA-MeCN	5	0	21
H	NMe_2	H	H	H_2O_2-AcOH	10	0	21
H	OMe	H	H	H_2O_2-AcOH	29	0	21,25
				MCPBA-$CHCl_3$	44	0	14
[5-Substituted Derivatives]							
H	H	Me	H	H_2O_2-AcOH	—		11
				MCPBA-$CHCl_3$	44		31
H	H	Ph	H	MCPBA-$CHCl_3$	37		31
H	H	OMe	H	H_2O_2-Na_2WO_4	61		29
				MCPBA-$CHCl_3$	70		30

(continued)

R_2	R_4	R_5	R_6	Method[a]	1-Oxide (%)	3-Oxide (%)	Reference
H	H	Cl	H	H_2O_2-AcOH-MoO_3	13		31
H	H	Br	H	H_2O_2-Na_2WO_4	19		29
				MCPBA-$CHCl_3$	15-29		30,31
[2,4-Disubstituted Derivataives]							
Me	Me	H	H	H_2O_2-AcOH	43.5[b]		23
				H_2O_2-AcOH	20[b]		22
				H_2O_2-AcOH	38	0	21
				MCPBA-$CHCl_3$	12	30	14
				MCPBA-$CHCl_3$	35	32	15
Me	Ph	H	H	H_2O_2-AcOH	24	0	14
				MCPBA-CH_2Cl_2	30	0	127
				MCPBA-$CHCl_3$	52	0	14
				H_2O_2-Na_2WO_4	60	0	26
Ph	Me	H	H	H_2O_2-AcOH	9	0	14
				MCPBA-$CHCl_3$	24	6	14
Ph	Ph	H	H	H_2O_2-AcOH	8	0	14
				MCPBA-$CHCl_3$	15	0	14
Me	OMe	H	H	H_2O_2-AcOH	25	0	22
				MCPBA-$CHCl_3$	60	0	14
Ph	OMe	H	H	MCPBA-$CHCl_3$	32	0	14
NH_2	Me	H	H	MCPBA-MeCN	7	46	21
NHMe	Me	H	H	MCPBA-MeCN	0	38	21
NH_2	Ph	H	H	H_2O_2-Na_2WO_4	44	0	122
NH_2	NH_2	H	H	H_2O_2-TFA	0	48	8
				MCPBA-dioxane	10	15	36
OMe	Me	H	H	H_2O_2-AcOH	30[b]		23
				MCPBA-$CHCl_3$	0		14
OMe	Ph	H	H	MCPBA-$CHCl_3$	0		14
OMe	OMe	H	H	MCPBA-$CHCl_3$	0		14
[4,6-Disubstituted Derivatives]							
H	Me	H	Me	H_2O_2-AcOH	75		18,19
				H_2O_2-AcOH	57		20
				MCPBA-MeCN	75		21
H	^tBu	H	^tBu	MCPBA-$CHCl_3$	42		99
H	Ph	H	Me	H_2O_2-AcOH	74		18,19
				H_2O_2-AcOH	76		22
				H_2O_2-Na_2WO_4	—		26
H	Ph	H	Ph	MPMA-$CHCl_3$	37		99
H	NH_2	H	Ph	H_2O_2-Na_2WO_4	0	30	123
H	NH_2	H	Me	MCPBA-MeCN	36		21
H	NHMe	H	Me	MCPBA-MeCN	33		21

(continued)

R_2	R_4	R_5	R_6	Method[a]	1-Oxide (%)	3-Oxide (%)	Reference
H	OMe	H	Me	H_2O_2-AcOH	66		23
				H_2O_2-AcOH	72		24
				H_2O_2-AcOH	70		21
H	OEt	H	Me	H_2O_2-AcOH	76		24
H	OBu	H	Me	H_2O_2-AcOH	77		24
H	OCH_2Ph	H	Me	H_2O_2-AcOH	70		24
H	OPh	H	Me	H_2O_2-AcOH	46		24
				MPPA-Et_2O	58		24
H	OMe	H	Ph	H_2O_2-AcOH	65		22
H	OEt	H	Ph	H_2O_2-AcOH	58		22
H	OPh	H	Ph	MPMA-$CHCl_3$	52		65
H	Cl	H	Me	MPMA-$CHCl_3$	30		58
H	Cl	H	Ph	MPMA-$CHCl_3$	26		58
H	Br	H	Ph	MPMA-$CHCl_3$	22		65
[2,5-Disubstituted Derivatives]							
Me	H	Ph	H	H_2O_2-AcOH	12		14
NH_2	H	Ph	H	H_2O_2-Na_2WO_4	27		105
[4,5-Disubstituted Derivatives]							
H	Me	Me	H	MCPBA-$CHCl_3$	23	36	31
H	Me	Ph	H	MCPBA-$CHCl_3$	9	18	31
H	Me	Cl	H	H_2O_2-AcOH-MoO_3	22	34	31
H	Me	Br	H	H_2O_2-AcOH-MoO_3	20	30	31
H	Me	OMe	H	MCPBA-$CHCl_3$	30	22	31
H	Ph	Me	H	MCPBA-$CHCl_3$	32	0	31
H	Ph	Ph	H	MCPBA-$CHCl_3$	26	0	31
H	Ph	Cl	H	H_2O_2-AcOH-MoO_3	41	0	31
H	Ph	OMe	H	MCPBA-$CHCl_3$	75	0	31
H	NH_2	Ph	H	H_2O_2-AcOH	0	43	123
				PMPBA-$CHCl_3$	0	30	123
H	OMe	Me	H	MCPBA-$CHCl_3$	68	0	31
H	OMe	Ph	H	MCPBA-$CHCl_3$	69	0	31
H	OMe	Cl	H	H_2O_2-AcOH-MoO_3	37	0	31
H	OMe	Br	H	H_2O_2-AcOH-MoO_3	36	0	31
H	OMe	OMe	H	MCPBA-$CHCl_3$	30	0	31
[2,4,6-Trisubstituted Derivatives]							
Me	Me	H	Me	H_2O_2-AcOH	33		11
Me	Et	H	Me	H_2O_2-AcOH	30	25	16,17
^{i}Pr	Et	H	Me	H_2O_2-AcOH	28	18	16,17
Me	CH_2Ph	H	Me	H_2O_2-AcOH	18	15	17
^{i}Pr	^{t}Bu	H	^{t}Bu	MPMA-$CHCl_3$	14	0	124
^{t}Bu	^{t}Bu	H	^{t}Bu	MPMA-$CHCl_3$	0	0	124

(continued)

R_2	R_4	R_5	R_6	Method[a]	1-Oxide (%)	3-Oxide (%)	Reference
Ph	Me	H	Me	H_2O_2-AcOH	45		17
Ph	Et	H	Me	H_2O_2-AcOH	22	12	17
Me	Ph	H	Me	H_2O_2-AcOH	40	0.6	17
Et	Ph	H	Me	H_2O_2-AcOH	44	0	15
Me	Ph	H	Et	H_2O_2-AcOH	31	0	15
Me	NH_2	H	Ph	MCPBA-acetone	0	40	123
				H_2O_2-Na_2WO_4	0	23	123
				H_2O_2-AcOH	0	21	123
				PMPBA-$CHCl_3$	0	40	123
Me	OCH_2Ph	H	Me	H_2O_2-AcOH	81	0	117
Me	OMe	H	Me	H_2O_2-AcOH	74	0	22
Me	OMe	H	Et	H_2O_2-AcOH	44	0	15
Me	OEt	H	Me	H_2O_2-AcOH	78	0	22
Me	OPr	H	Me	H_2O_2-AcOH	78	0	22
Me	O^{i}Pr	H	Me	H_2O_2-AcOH	73	0	22
Me	OPh	H	Me	H_2O_2-AcOH	5	0	22
^{i}Pr	OMe	H	Me	H_2O_2-AcOH	74	0	22
^{i}Pr	OEt	H	Me	H_2O_2-AcOH	67	0	22
^{i}Pr	OPr	H	Me	H_2O_2-AcOH	73	0	22
^{i}Pr	O^{i}Pr	H	Me	H_2O_2-AcOH	60	0	22
CH_2OMe	OMe	H	Me	MCPBA-$CHCl_3$	42	0	112
Me	OPh	H	NH_2	MCPBA-acetone	31	0	123
				MCPBA-$CHCl_3$	39	0	123
Me	OMe	H	CH_2OMe	MCPBA-$CHCl_3$	51	0	112
Me	Cl	H	Me	MCPBA-CH_2Cl_2	65	0	33
				MPMA-$CHCl_3$	34	0	32
Et	Cl	H	Me	MPMA-$CHCl_3$	57	0	32
^{i}Pr	Cl	H	Me	MPMA-$CHCl_3$	74	0	32
Cl	Me	H	Me	MPMA-$CHCl_3$	34		102
OMe	OMe	H	Me	H_2O_2-AcOH	42[b]		23
NH_2	NH_2	H	Me	H_2O_2-TFA	0	64	9
NH_2	NH_2	H	Cl	90%H_2O_2-TFA	0	64	5
NH_2	NH_2	H	SO_2Ph	70%H_2O_2-TFA	0	60[d]	6
NH_2	NH_2	H	OAr	MCPBA-EtOH	—		125
Ph	OAr	H	NH_2	MCPBA-AcOH	44	0	126
NH_2	Me	H	Me	H_2O_2-AcOH	20		122
				H_2O_2-AcOH	60		56
NH_2	Ph	H	Me	H_2O_2-Na_2WO_4	56	0	105
				H_2O_2-AcOH	45	0	56

(continued)

R_2	R_4	R_5	R_6	Method[a]	1-Oxide (%)	3-Oxide (%)	Reference
[2,4,5-Trisubstituted Derivatives]							
NH_2	NH_2	Et	H	H_2O_2-TFA	0	68	9
NH_2	NH_2	CH_2OMe	H	MCPBA-dioxane	25	27	36
NH_2	NH_2	CH_2OAr	H	MCPBA-CH_2Cl_2	25	18	60
[4,5,6-Trisubstituted Derivatives]							
H	Cl	Ph	Ph	MPMA-$CHCl_3$	42	0	65
[2,4,5,6-Tetrasubstituted Derivatives]							
NH_2	NH_2	NO_2	NH_2	H_2O_2-TFA	28[e,f]		4
NH_2	NHEt	NO_2	NH_2	H_2O_2-TFA	68[g]		6
NH_2	NHPh	NO_2	NH_2	H_2O_2-TFA	51[e]		6
NH_2	NMePh	NO_2	NH_2	H_2O_2-TFA	7.2[g]		6
NH_2	Cl	Et	NH_2	MCPBA-EtOH	71		9
NH_2	Cl	Cl	NH_2	90%H_2O_2-TFA	80		5
Me	NH_2	NO_2	NH_2	H_2O_2-TFA	51[e]		57

a) MCPBA: m-chloroperbenzoic acid; MPMA: monopermaleic acid (H_2O_2-maleic anhydride); MPPA: monoperphthalic acid (H_2O_2-phthalic anhydride); PMPBA: p-methylperbenzoic acid; TFA: trifluoroacetic acid.

b) The position of the N-oxide group was not determined.

c) 1-oxide:3-oxide=2:7.

d) Yield from phenylthio derivative.

e) Yields from 5-nitroso derivatives.

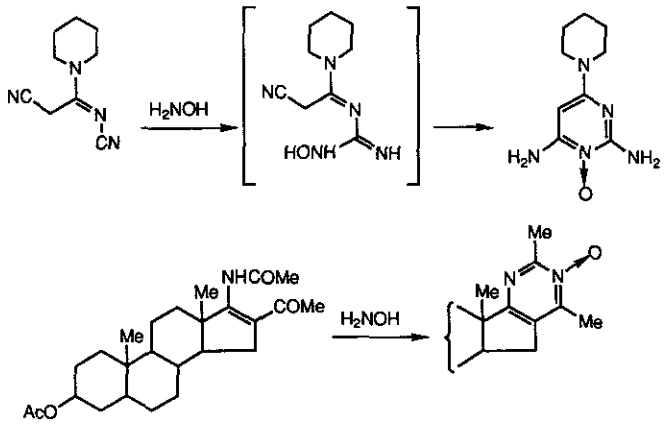
f) Di-N-oxide: 48%.

g) Yields from 5-nitro derivatives.

III. SYNTHESES OF PYRIMIDINE N-OXIDES BY OTHER METHODS

A. By Ring-Closure Reactions

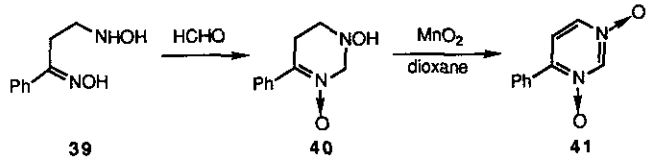
It is well known that the condensation of glutacondialdehyde sodium salt with ammonium acetate gives rise to pyridine.[43] When hydroxylamine is used instead of ammonium acetate, pyridine 1-oxide is formed.[44] There are a few examples of pyrimidine N-oxides being formed by ring closures of this type: typical ones are illustrated in Scheme 11.[45,46]



Scheme 11

This route seems to be promising as an unequivocal synthesis of unsymmetrical dialkyl- and trialkylpyrimidine N-oxides, but such application is not available in the literature.

It is of interest that the condensation of the β-hydroxyaminopropiophenone oxime (**39**) with formaldehyde followed by oxidation with manganese dioxide afforded the 4-phenylpyrimidine 1,3-dioxides (**41**).[47,48] Unsubstituted,[47,48] 4,6-disubstituted,[49] and 2,4,6-trisubstituted pyrimidine 1,3-dioxides[50] were also synthesized by this method. The synthesis of pyrimidine 1,3-dioxides by means of N-oxidation has not been reported except in the case of polyaminopyrimidines (Section II,E), so cyclizations of this type are expected to open a new field of pyrimidine N-oxide chemistry.

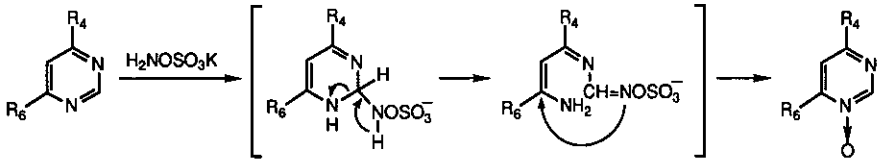


39 **40** **41**

Scheme 12

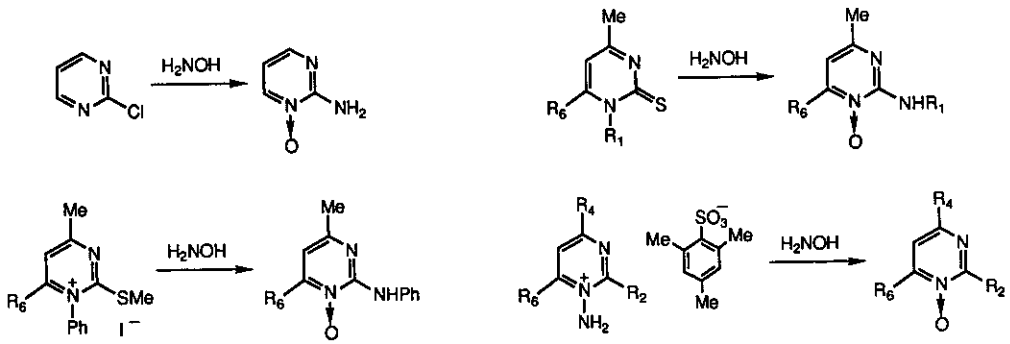
B. By Ring-Transformation Reactions

When 4-substituted pyrimidines were allowed to react with potassium hydroxylamine-O-sulfonate, the corresponding pyrimidine N-oxides were obtained.[51] The proposed reaction mechanism involved an initial attack of hydroxylamine at the 2-position of the substrates. The subsequent ring-opening and recyclization reactions seemed to be reasonable as shown in Scheme 13, but an alternative explanation starting from an initial attack at the 4-(or 6-)position is also possible. In general, the pyrimidine ring is highly susceptible to nucleophilic attack at the 4-(or 6-)position even in 4,6-disubstituted derivatives, so the reported mechanism is now considered to be only tentative.



Scheme 13

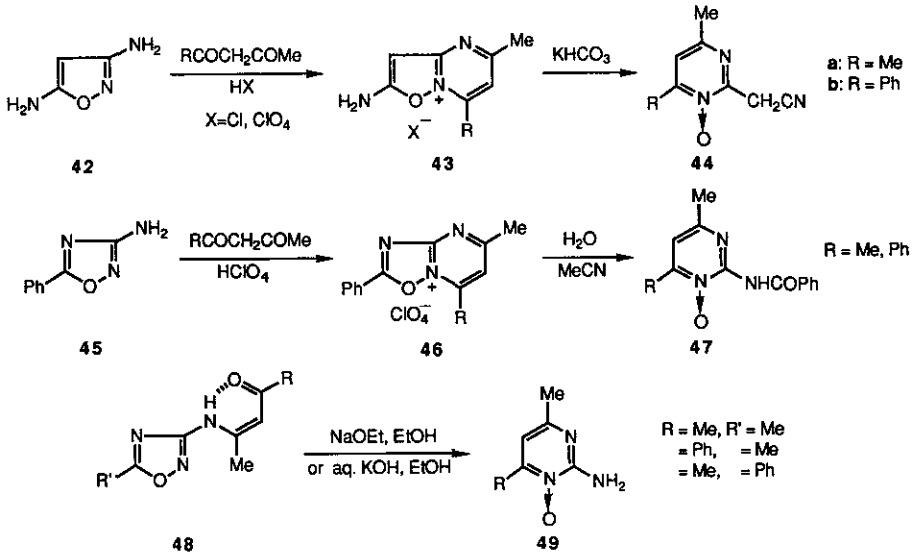
There are several examples of pyrimidine mono-N-oxide formation through a ring-transformation reaction, as illustrated in Scheme 14.[52-54] The mechanism of these ring-transformation reaction can be explained by assuming the initial attack of hydroxylamine at position 4(or 6), a subsequent ring-opening, and a final recyclization to the N-oxides.



Scheme 14

The reaction of 3,5-diaminoisoxazole (**42**) with acetylacetone resulted in the formation of the isoxazolo[2,3-a]pyrimidinium salt (**43a**) which was converted to 4,6-dimethylpyrimidine-2-acetonitrile 1-oxide (**44**) under basic conditions;[55] benzoylacetone could also be employed in this reaction. Thus the reaction is an interesting method for the preparation of pyrimidine-2-acetonitrile 1-oxides (**44**). Recently, a similar ring-transformation reaction into 2-aminopyrimidine 1-oxides

has been reported.[56,57] Thus, 3-amino-5-phenyl-1,2,4-oxadiazole (**45**) reacted with 1,3-diketones in the presence of perchloric acid to give oxadiazolopyrimidinium derivatives (**46**) which were transformed into 6-substituted 2-benzoylamino-4-methylpyrimidine 1-oxides (**47**) by treatment with water. The oxadiazolylenaminoketones (**48**) were also converted into the corresponding 2-aminopyrimidine 1-oxides (**49**) under basic conditions.[56]



Scheme 15

C. By Conversion of the Substituents

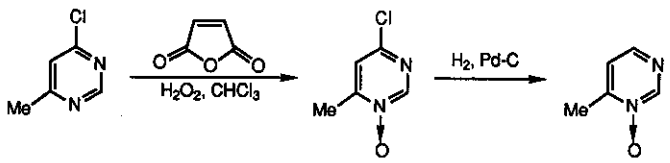
As described in Section II,F, there are various restrictions, such as oxidation or hydrolysis of the substrates, to any synthesis of pyrimidine N-oxide derivatives. Accordingly, conversion of one substituent on a pyrimidine N-oxide to another has *synthetic advantage in some cases.* For example, 2-(or 4-)alkyl(or aryl)thiopyrimidine N-oxides have been synthesized usually from 2-(or 4-)chloro- or 2-(or 4-)phenoxypyrimidine N-oxides by a nucleophilic substitution, simply because 2-(or 4-)alkyl(or aryl)thiopyrimidines do not undergo N-oxide formation without complication (see Section II,F,1). Further examples of pyrimidine N-oxide synthesis by nucleophilic reaction are described in Section VI.

Conversion of the methyl group of 4-methyl-6-phenylpyrimidine 1-oxide into a styryl or formyl group is another example in this category; these types of conversion are discussed in detail in Section X,B.

IV. STRUCTURAL DETERMINATION OF PYRIMIDINE N-OXIDES

A. By Measurements of Dipole Moments

The two basic nitrogen atoms in a pyrimidine ring give rise to a troublesome problem in the structural elucidation of pyrimidine mono-N-oxides. In 1964, Ogata et al.[13] reinvestigated the N-oxidation of 4-methylpyrimidine (**3**) and isolated the 1-oxide (**4**) and the 3-oxide (**5**) (see Section II,B). They determined the position of the N-oxide group in each isomer by comparison of the observed and calculated values for the dipole moment of each N-oxide. Later, van der Plas et al.[58] confirmed the above results by a chemical method: they converted 4-chloro-6-methylpyrimidine 1-oxide (**51**), obtained by the N-oxidation of **50**, into 4-methylpyrimidine 3-oxide (**5**) by catalytic hydrogenolysis.



50 **51** **5**

Scheme 16

Ogata et al.[59] also proved the structure of 4-ethoxy-6-methylpyrimidine N-oxide as the 1-oxide by measurement of its dipole moment. Although the possible presence of conformers, due to the free rotation of the 4-alkoxyl group, made the calculation complicated, the observed value was in rough accord with the calculated value of the cis-conformer of the 1-oxide.

B. By Proton Magnetic Resonance Spectroscopy

In general, the ^{1}H-nmr spectra of simple pyrimidine derivatives are not much affected by introduction of the N-oxide group. For example, the ^{1}H-nmr spectral data for 4-ethyl-2,6-dimethylpyrimidine 1-oxide (**52**) and the 3-oxide (**53**) were not inconsistent with pyrimidine N-oxide structures, but they gave no information to distinguish the 1-oxide (**52**) from the 3-oxide (**53**).[17]

When the ^{1}H-nmr spectrum of 4-ethoxy-6-methylpyrimidine 1-oxide was measured in $CDCl_3$ in the presence of tris(heptafluorobutanoylpivaloylmethanato)europium [$Eu(fod)_3$],[16,17] a large displacement of the chemical shifts was observed for the signal of the 6-methyl group, whereas the other singals appeared with relatively small displacements. The results clearly demonstrated that the lanthanide reagent coordinates to the N-oxide group predominantly and that the chemical shifts of the protons in the neighborhood of the N-oxide group are affected by the lanthanide

reagent to show a large down-field shift. In this manner, the identification of the 1-oxide and the 3-oxide has become easy work.

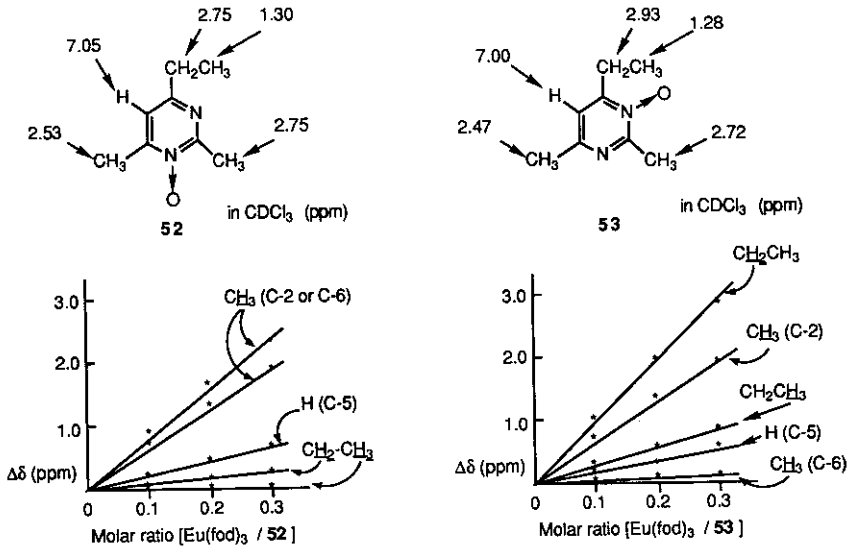


Fig. 1

C. By X-Ray Crystallographic Analysis

There are two reports on the X-ray crystallographic analysis of the N-oxides obtained by N-oxidation of 2,4-diaminopyrimidines.[60,61] In many cases, however, simple pyrimidine mono-N-oxides are liquids or hygroscopic solids, and it is not easy as rule to transform them into crystalline derivatives suitable for crystallographic analysis. Accordingly, the use of X-ray crystallography is not generally applicable to the structural determination of pyrimidine N-oxides.

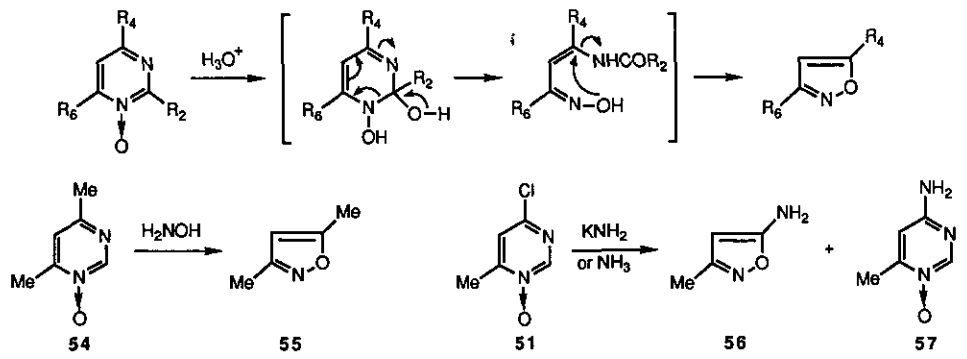
V. REACTIONS BY NUCLEOPHILIC PROCESSES

A. Ring-Transformation Reactions

Unlike other diazine N-oxides, pyrimidine N-oxides tend to undergo ring-cleavage reactions by the attack of various nucleophilic reagents. For example, 4-phenylpyrimidine 1-oxide was converted into 5-phenylisoxazole by heating with hydrochloric acid in good yield.[62] Under similar conditions, 4-ethyl-2,6-dimethylpyrimidine 1-oxide and 3-oxide were converted into 5-ethyl-3-methyl- and 3-ethyl-5-methylisoxazole, respectively.[16,17] Hydration of the pyrimidine ring and subsequent ring-opening are considered to be the key steps in the ring-transformation.

Two other ring-transformations of pyrimidine N-oxides into isoxazoles have been reported by van der Plas et al. The first example involved reaction of 4,6-dimethylpyrimidine 1-oxide (**54**) with hydroxylamine to give 3,5-dimethylisoxazole (**55**) as the sole product.[63] As the initial step of this reaction, hydroxylamine attacks at the 6-position of the pyrimidine ring.

The second example was the reaction of 4-chloro-6-methylpyrimidine 1-oxide (**51**) in liquid ammonia, with (or without) potassium amide, from which 5-amino-3-methylisoxazole (**56**) was isolated as the major product together with a small amount of 4-amino-6-methylpyrimidine 1-oxide (**57**).[58,64,65] Using the ^{15}N-labeled substrate, it was shown that nucleophilic attack of amide ion at the 2-position was the trigger of this reaction.

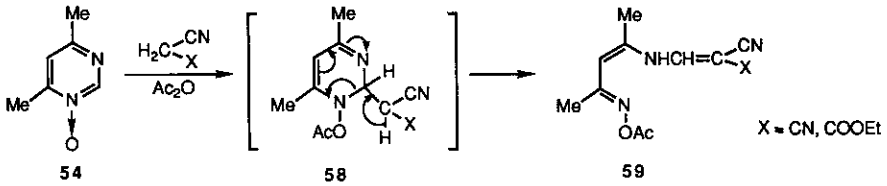


Scheme 17

B. Reactions with Active Methylene Compounds

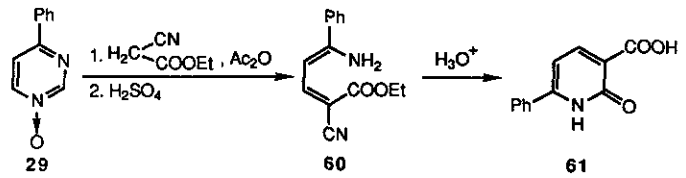
Quinoline 1-oxide is known to react with active methylene compounds in the presence of acetic anhydride,[66] thereby providing one of the useful methods for preparing 2-substituted quinolines. In contrast, when 4,6-dimethylpyrimidine 1-oxide (**54**)

was treated under the same conditions, the ring-opened products (**59**) were obtained instead of the 2-substituted pyrimidines.[67] The ring-opening reaction is considered to be initiated by attack of the nucleophiles at the 2-position of the pyrimidine ring.



Scheme 18

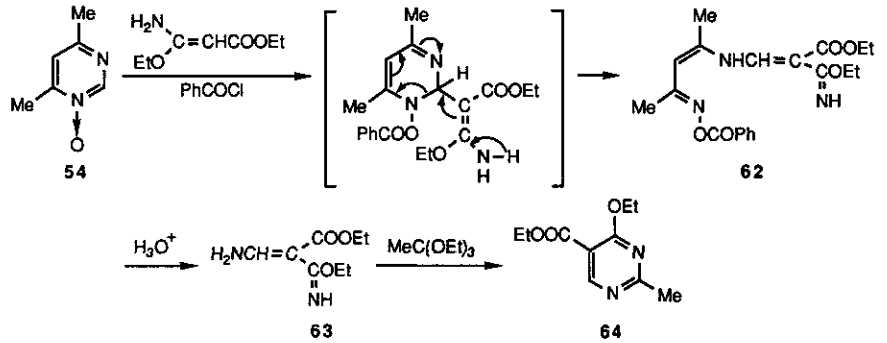
The reaction of 4-phenylpyrimidine 1-oxide (**29**) with ethyl cyanoacetate gave a similar ring-opened product, ethyl 5-amino-2-cyano-5-phenyl-2,4-pentadienoate (**60**).[68] The structure of this product was elucidated by its trasformation into 2-oxo-6-phenyl-1,2-dihydropyridine-3-carboxylic acid (**61**). In this ring-cleavage reaction, the reagent is considered to attack the 6-position of the N-oxide.



Scheme 19

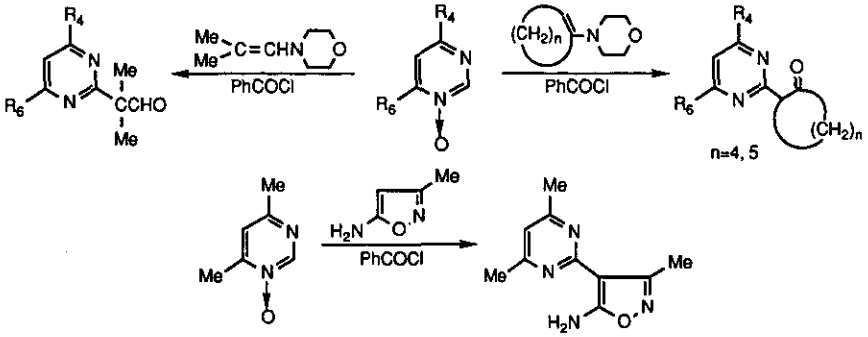
C. Reactions with Enamines

4,6-Dimethylpyrimidine 1-oxide (**54**) smoothly reacted with ethyl 3-amino-3-ethoxyacrylate in the presence of benzoyl chloride to give an open-chain compound (**62**) which was transformed into *ethyl 4-ethoxy-2-methylpyrimidine-5-carboxylate* (***64***) via the aminomethyleneacetimidate (**63**).[67]



Scheme 20

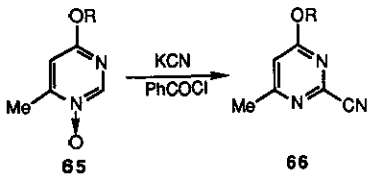
In contrast, the reaction of 4,6-disubstituted pyrimidine 1-oxides with various morpholine enamines in the presence of benzoyl chloride gave pyrimidine derivatives having a carbon-substituent at the 2-position.[69] When 4-phenylpyrimidine 1-oxide was employed, the reaction took place at the 2-position exclusively, and α,α-dimethyl-4-phenylpyrimidine-2-acetaldehyde was obtained without concomitant formation of the 6-isomer.[28] In these cases, the behavior of pyrimidine N-oxides resembles that of quinoline N-oxides.[70,71] Furthermore, it has been reported that 5-amino-3-methylisoxazole can be employed as an enamine.[67]



Scheme 21

D. Reissert-Henze Type Reactions

It is well known that the reaction of quinoline 1-oxide with potassium cyanide in the presence of benzoyl chloride (Reisssert-Henze reaction) affords quinoline-2-carbonitrile,[72] while many pyridine 1-oxides, except 4-chloro-[73] and trifluoromethylpyridine 1-oxides,[74] are unaffected by such treatment. Unlike pyridine 1-oxides, however, pyrimidine N-oxides are susceptible to the Reissert-Henze reaction.[23-25] For example, 4-alkoxy-6-methylpyrimidine 1-oxides (**65**) were readily transformed into 4-alkoxy-6-methylpyrimidine-2-carbonitriles (**66**).[24]



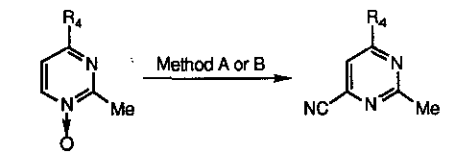
65 **66**

Scheme 22

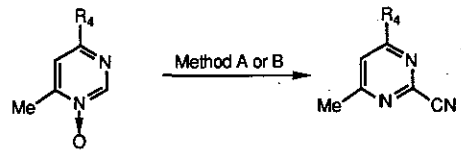
In the cases of 4-methyl- and 2,4-dimethylpyrimidine N-oxide, the yields of the corresponding pyrimidinecarbonitriles were poor.[23] Recently Vorbrüggen et al. have reported a modified Reissert-Henze reaction using trimethylsilyl cyanide (TMSCN) as the cyanating reagent. Thus, this procedure has open a ready route to pyridine-

2-carbonitriles from pyridine 1-oxides.[75] In a series of alkylpyrimidine N-oxides, the modified method[76] brought about much better results than the conventional method,[23-25,28] as shown below.

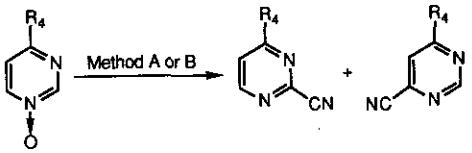
It should be mentioned that the presence of electron-donating substituents at the 4-position facilitates nucleophilic attack at the 2-position in many pyrimidine reactions. For example, the reaction of 4-methoxypyrimidine 1-oxide under these conditions gave 4-methoxypyrimidine-2-carbonitrile exclusively.[76] A similar effect to this site-selectivity was observed in the modified Reissert-Henze reaction of 5-substituted 4-methoxypyrimidine 1-oxides.[31]



R_4	Method A	Method B
=H		71%
=Me	1.4%	81
=Ph		90
=OMe		0



R_4	Method A	Method B
=H		71%
=Me	53%	87
=Ph	51	90
=OMe	90	87

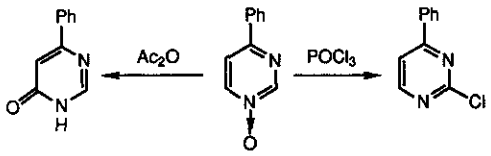


R_4	Method A	Method B
=H		75%(2-CN:6-CN=2:3)
=Me	1.9%(2-CN)	74 (2-CN)
	0 (6-CN)	0 (6-CN)
=Ph	88	21 (2-CN)
	(2-CN:6-CN=2:1)	55 (6-CN)
=OMe	76 (2-CN)	86 (2-CN)
	0 (6-CN)	0 (6-CN)

Method A : KCN, PhCOCl, H_2O, $CHCl_3$
Method B : TMSCN, Et_3N, MeCN

Scheme 23

Other than the cyanation of pyrimidine N-oxides, some reactions with a similar mechanism have been reported.[19,22,23,28] For example, the reaction of 4-phenylpyrimidine 1-oxide (**29**) with phosphoryl chloride gave 2-chloro-4-phenylpyrimidine (**67**),[28] whereas the reaction of **29** with acetic anhydride afforded 4-phenyl-6(1H)-pyrimidinone (**68**) as the sole product.[22] It is of interest that such a difference in site-selectivity appears in the same substrate, although the reason is not clear at present.

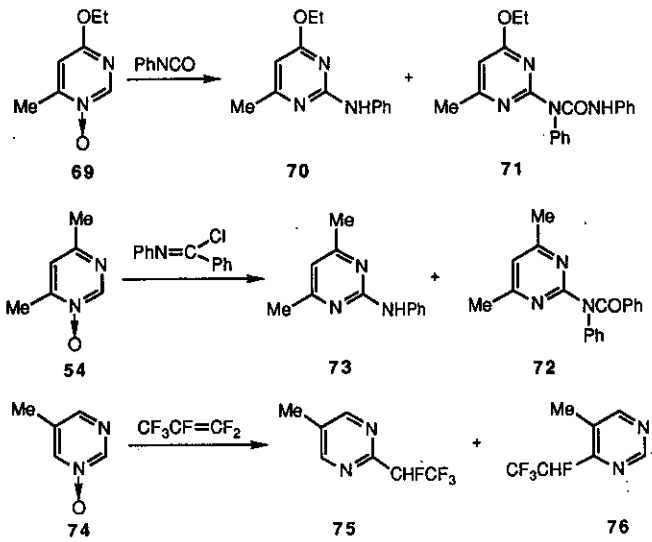


68 **29** **67**

Scheme 24

E. Cycloaddition Reactions

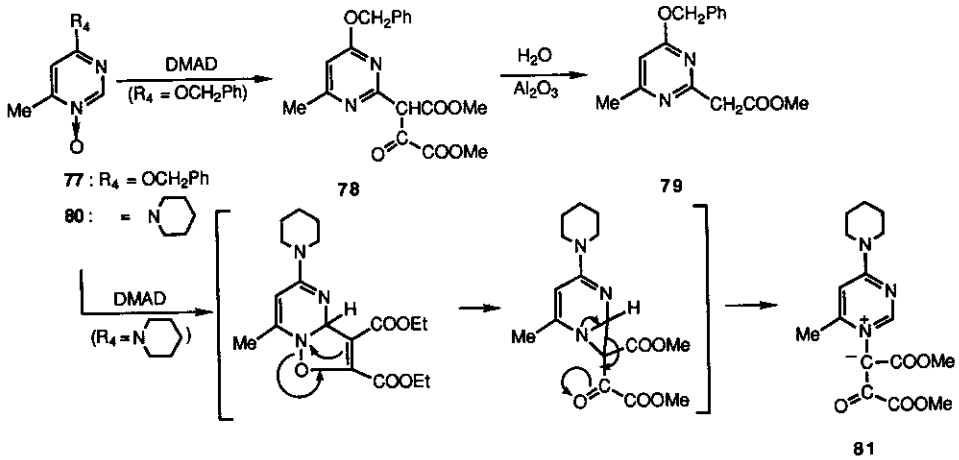
Huisgen et al. have reported that the reaction of pyridine 1-oxide with phenyl isocyanate afforded 2-anilinopyridine.[77] Hamana et al.[78] described the formation of methyl α-formylquinoline-2-acetate from the reaction of quinoline 1-oxide with methyl propynoate. In these reactions, pyridine and quinoline 1-oxides act as 1,3-dipolar compounds. The 1,3-dipolar cycloaddition of heteroaromatic N-oxides, however, frequently gives complicated results due to subsequent sigmatropic rearrangements.[79] Similar aspects appear in the reaction of pyrimidine N-oxides. One such example was the reaction of 4-ethoxy-6-methylpyrimidine 1-oxide (**69**) with excess phenyl isocyanate, which gave 2-anilino-4-ethoxy-6-methylpyrimidine (**70**) together with the 2-ureidopyrimidine (**71**), derived from the reaction of **70** with the remaining phenyl isocyanate.[80,81] Other examples were the reaction of 4,6-dimethylpyrimidine 1-oxide (**54**) with α-chlorobenzylideneaniline[82] and the reaction of 5-methylpyrimidine 1-oxide (**74**) with hexafluoropropene,[83] both of which are outlined in Scheme 25.



Scheme 25

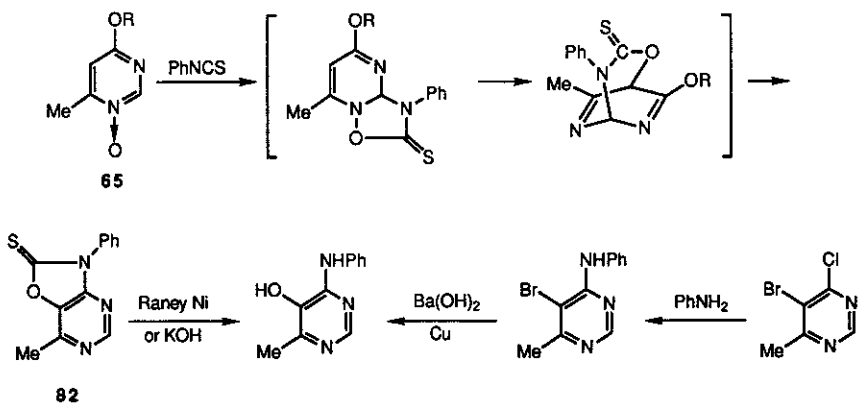
The reaction of 4-benzyloxy-6-methylpyrimidine 1-oxide (**77**) with dimethyl acetylenedicarboxylate (DMAD), like that of quinoline 1-oxide, gave a simple addition-elimination product (**78**) which was easily hydrolyzed to methyl 4-benzyloxy-6-methylpyrimidine-2-acetate (**79**).[80,84] In the case of 6-methyl-4-piperidinopyrimidine 1-oxide (**80**), however, the reaction resulted in the formation of a betain type product (**81**) instead of methyl 6-methyl-4-piperidino-

pyrimidine-2-acetate.[84] A similar result has been reported for the reaction of phenanthridine 5-oxide with DMAD.[85]



Scheme 26

In contrast to the above reactions, the use of phenyl isothiocyanate as a 1,3-dipolarophile on 4-alkoxy-6-methylpyrimidine 1-oxides (**65**) gave the products (**82**) through a double 1,3-sigmatropic rearrangement.[80,81] Thus the reaction of **65** with phenyl isothiocyanate, regardless of the kind of 4-alkoxyl groups, afforded **82**. The structure of the product was established as 7-methyl-3-phenyl-2,3-dihydrooxazolo[4,5-d]pyrimidine-2-thione (**82**) by a chemical method. A likely mechanism for the reaction is shown in Scheme 27, although its details remain to be elucidated.

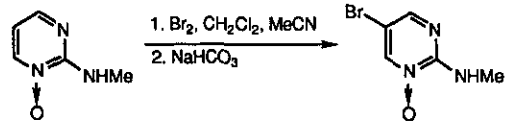


Scheme 27

VI. REACTIONS BY ELECTROPHILIC PROCESSES

A. Halogenation and Related Reactions

Pyrimidine N-oxides which have at least one amino group can be halogenated at the 5-position by a simple electrophilic process. For example, 2,6-diamino-4-chloropyrimidine 1-oxide (**18**) was chlorinated at the 5-position with chlorine,[5] and bromination of 2-methylaminopyrimidine 1-oxide (**83**) with bromine gave 5-bromo-2-methylaminopyrimidine 1-oxide (**84**) in 93% yield.[86]

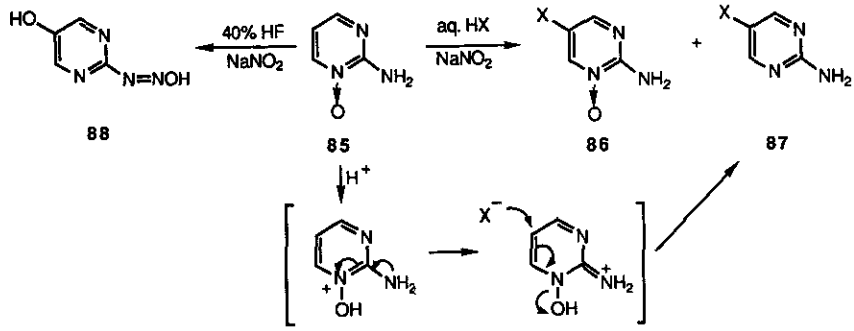


83 **84**

Scheme 28

The reaction of 2-aminopyrimidine 1-oxide (**85**) with sodium nitrite in hydrochloric or hydrobromic acid yielded 2-amino-5-halopyrimidine 1-oxides (**86**) and their deoxygenated products (**87**) without diazotization of the amino group.[87] The former products (**86**) are formed by electrophilic halogenation with the active species generated from hydrochloric or hydrobromic acid and sodium nitrite. The latter compounds (**87**) are formed by nucleophilic addition of the halide ion to the protonated substrates and a subsequent dehydration as shown below.

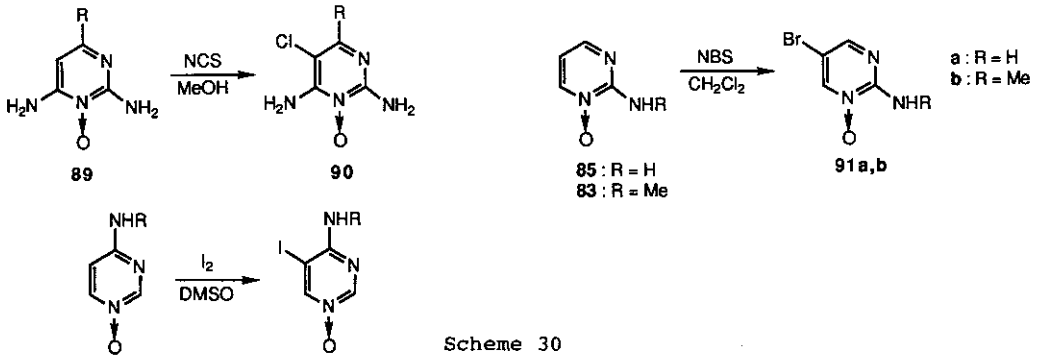
A similar halogenation of 2-amino-4-phenylpyrimidine 1-oxide has been reported, but in this case, no deoxygenated product was isolated.[87] When 2-aminopyrimidine 1-oxide (**85**) was treated with 40% hydrofluoric acid and sodium nitrite, 5-hydroxy-2-hydroxyazopyrimidine (**88**) was obtained.[88] The reaction pathway seems to be similar to the deoxygenative halogenation described above. On the other hand, 2,4-diamino-6-ethylaminopyrimidine 1-oxide was not chlorinated or hydroxylated under similar conditions, but 2,4-diamino-6-ethylamino-5-nitroso-pyrimidine 1-oxide was obtained.[6]



88 **85** **86** **87**

Scheme 29

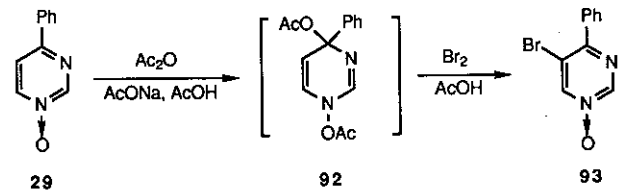
N-Halosuccinimides were also employed as halogenating agents. Namely, 2,6-diaminopyrimidine 1-oxides (**89**) are chlorinated with N-chlorosuccinimide (NCS) in methanol[60] and 2-amino- (**85**) and 2-methylaminopyrimidine 1-oxide (**83**) are brominated with N-bromosuccinimide (NBS) in dichloromethane in high yields.[86] It has also been reported that **83**, **85**, and 4-aminopyrimidine 1-oxides are easily iodinated with iodine in dimethyl sulfoxide.[89]



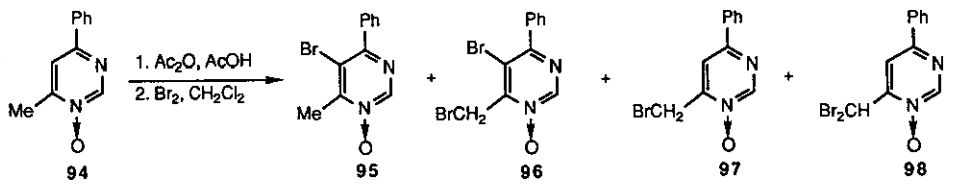
89 **90** **85**: R = H; **83**: R = Me **91a,b**

Scheme 30

Another characteristic bromination of pyrimidine N-oxides has been reported.[26] When 4-phenylpyrimidine 1-oxide (**29**) was allowed to react with bromine in the presence of acetic anhydride and sodium acetate in acetic acid, 5-bromo-4-phenylpyrimidine 1-oxide (**93**) was obtained in 40% yield. The intermediate of this reaction was 1,4-diacetoxy-4-phenyl-1,4-dihydropyrimidine (**92**) which was electrophilically brominated to give the final product (**93**). The bromination of 6-methyl-4-phenylpyrimidine 1-oxide (**94**) gave the 5-bromo-6-methyl-4-phenylpyrimidine 1-oxide (**95**) and 5-bromo-6-bromomethyl-4-phenylpyrimidine 1-oxide (**96**) together with the compounds brominated only at the methyl group (**97**,**98**). On the other hand, 2-methyl-4-phenylpyrimidine 1-oxide did not give 5-brominated derivatives but the bromomethyl and dibromomethyl derivatives.



29 **92** **93**



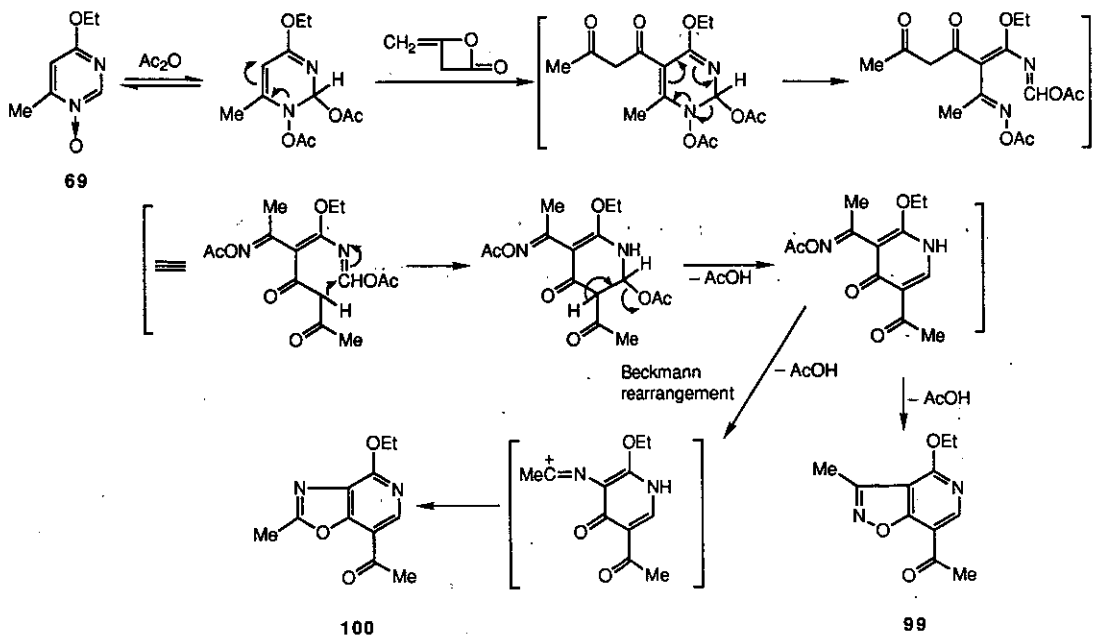
94 **95** **96** **97** **98**

Scheme 31

B. Reaction with Diketene

When pyridine 1-oxide is treated with diketene (4-methylene-2-oxetanone), the diketene is completely dimerized to dehydroacetic acid, while pyridine 1-oxide remains unchanged.[90] On the contrary, quinoline 1-oxide reacts with diketene in acetic acid to give 2,6-dimethyl-3-(2-quinolyl)-4-pyrone as the sole product.[91] The reaction of isoquinoline 2-oxide with diketene under similar conditions gives a benzoquinolizidine derivative and a dihydroisoquinoline derivative together with 3-(1-isoquinolyl)-2,6-dimethyl-4-pyrone.[92]

On the basis of these results, the reaction of diketene with heteroaromatic N-oxides seems to be flexible, according to the nature of the starting N-oxides. In fact, 4-ethoxy-6-methylpyrimidine 1-oxide (**69**) reacted with diketene in acetic anhydride to give two isomeric products, 7-acetyl-4-ethoxy-3-methylisoxazolo-[4,5-c]pyridine (**99**) and 7-acetyl-4-ethoxy-2-methyloxazolo[4,5-c]pyridine (**100**).[93] The likely mechanism of this ring-transformation is analogous with that of the bromination in acetic anhydride described in Section VI,A. Further, **100** may be formed via the Beckmann rearrangement of a 4-pyridone-type intermediate.

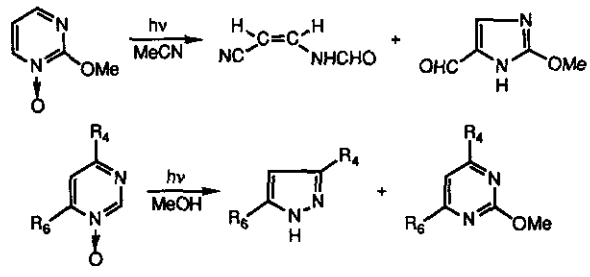


69 **100** **99**

Scheme 32

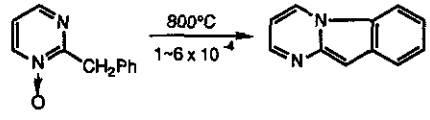
VII. PHOTOCHEMICAL REACTIONS AND FLASH PYROLYSES

There are scattered papers dealing with photochemical reaction of pyrimidine N-oxides.[94-99] Although some interesting observations have been reported, synthetically useful results have not been obtained until now. The ring-opening reaction and the concomitant formation of imidazole derivatives under irradiation are considered to be characteristics of pyrimidine N-oxides.



Scheme 33

There exists a paper in which the flash pyrolysis of 2- and 6-benzylpyrimidine 1-oxides at 800°C were reported to give indolopyrimidine derivatives.[100]



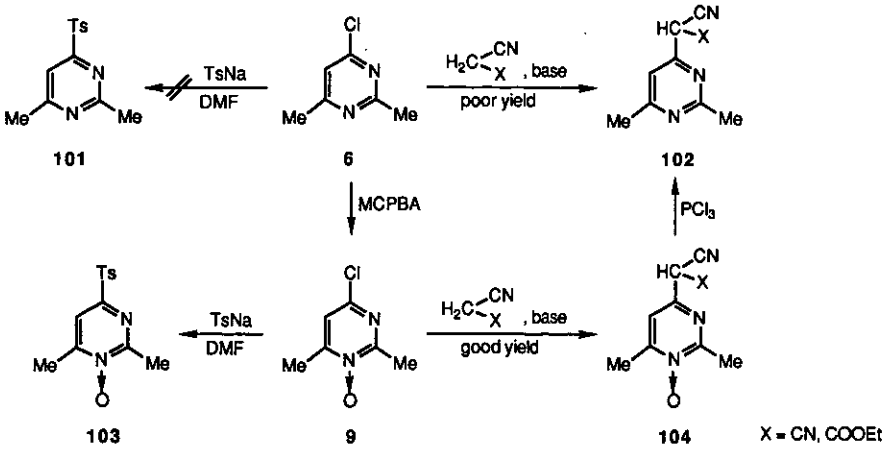
Scheme 34

VIII. EFFECT OF AN N-OXIDE GROUP ON THE REACTIVITY OF SUBSTITUENTS

A. Acceleration of Aromatic S_N2 Substitution Reactions

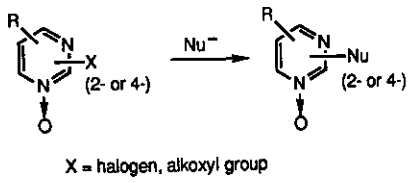
Okamoto et al.[101] measured the rate of nucleophilic substitution of 4-chloroquinoline and its 1-oxide with piperidine; they found that the presence of the N-oxide function facilitated the reactivity of the chloro substituent at the 4-position.

Rate constants for the nucleophilic substitution of 4-chloropyrimidine 1-oxide have not been measured to date but chemical evidence suggests a higher reactivity for chloropyrimidine N-oxides than for the corresponding chloropyrimidines.[33] Thus 4-chloro-2,6-dimethylpyrimidine 1-oxide (**9**) smoothly reacted with sodium p-toluenesulfinate to give 2,6-dimethyl-4-tosylpyrimidine 1-oxide (**103**) in good yield, whereas 4-chloro-2,6-dimethylpyrimidine (**6**) was recovered under the same conditions. The reaction of **6** and **9** with active methylene compounds, shown in Scheme 35, are other examples.



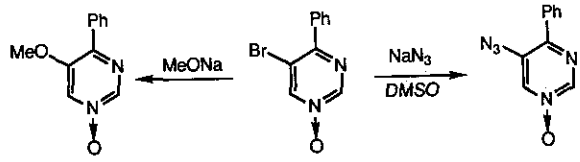
Scheme 35

The following reactions also suggest an activating effect by an N-oxide group on nucleophilic substitutions, although these have not been compared with those of corresponding halopyrimidines. Thus 2- or 4-chloropyrimidine 1-oxides easily reacted with sodium alkoxides,[32,49] imidazole,[102] ammonia,[9] trimethylamine,[65] thiophenol,[6,65] or hydriodic acid[65] to give the corresponding substitution products. Furthermore, 4-alkoxypyrimidine 1-oxides and especially 4-phenoxypyrimidine 1-oxides, were easily converted into other 4-alkoxy-,[22,103] 4-dialkylamino-,[15,103] or 4-phenylthiopyrimidine 1-oxides.[103]



Scheme 36

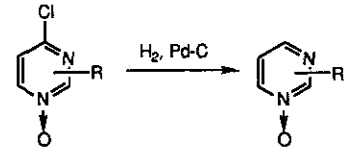
The activating effect of an N-oxide group on nucleophilic substitutions has also been demonstrated by the reaction of several 5-bromopyrimidine 1-oxides with nucleophiles, while 5-bromopyrimidines are known to be unreactive towards nucleophilic reactions. For example, 5-bromo-4-phenylpyrimidine 1-oxide (**93**) reacted with sodium methoxide[26] or sodium azide[104] to give the 5-methoxy and 5-azido compound, respectively. 5-Dimethylaminopyrimidine 1-oxide was obtained by the reaction of 5-bromopyrimidine 1-oxide with dimethylamine under conventional conditions.[29]



93

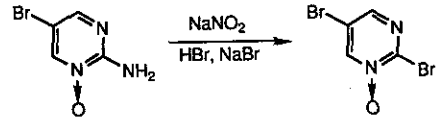
Scheme 37

Hydrogenation of 4-chloropyrimidine 1-oxides over palladium-charcoal to give pyrimidine 1-oxides is considered to be an additional example of nucleophilic substitution reactions.[8,9,58,65] In this reaction, the N-oxide group was not deoxygenated before dehalogenation (see Section X).



Scheme 38

When 2-amino-5-bromopyrimidine 1-oxide (**91a**) was treated with sodium nitrite in the presence of hydrobromic acid and sodium bromide, 2,5-dibromopyrimidine 1-oxide (**105**) was obtained, but the yield was unsatisfactory.[87] 2,5-Dichloropyrimidine 1-oxide[87] and 2-chloro-4-phenylpyrimidine 1-oxide[105] were gotten in a similar manner.



91a **105**

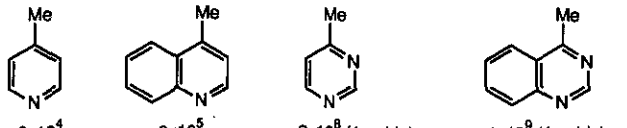
Scheme 39

Some of the nucleophilic reactions described above are useful to synthesize pyrimidine N-oxides which cannot be obtained by direct N-oxidation (see Section III) or by cyclization methods (see Sections IV,A and IV,B).

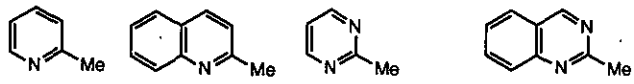
B. Activating Effect on α- and γ-Methyl Groups

The acidity of methyl groups attached to six-membered N-heteroaromatic rings can be roughly estimated by measurement of the time-dependent decrease of peak intensity of ^{1}H-nmr signals due to the methyl group in deuterium oxide under basic conditions.[106] The relative rates for hydrogen-deuterium exchange within each methyl group are listed in the next page.

Table III. Relative Rate Constants for Hydrogen-Deuterium Exchange within the Methyl Groups of Monomethylazines and Their N-Oxides



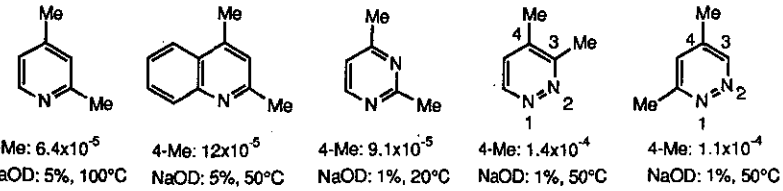
N-Oxide	6×10^{4}	8×10^{5}	2×10^{8} (1-oxide) 3×10^{9} (3-oxide)	1×10^{9} (1-oxide) 4×10^{8} (3-oxide)
Free base	8x10	3×10^{3}	2×10^{6}	1×10^{8}



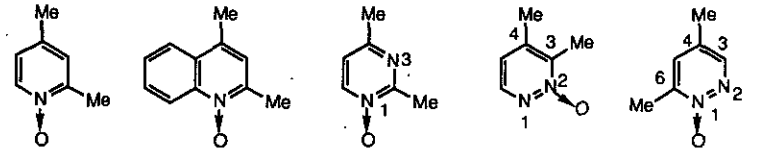
N-Oxide	1×10^{5}	1×10^{7}	3×10^{7}	9×10^{7} (3-oxide)
Free base	1.0	1×10^{3}	2×10^{6}	1×10^{8}

On the basis of these values, it is concluded that the N-oxide group introduced into six-membered N-heteroaromatics enchances the acidity of the adjacent methyl groups in particular. For example, the introduction of an N-oxide group into 2,4-dimethylpyridine and 2,4-dimethylquinoline made the 2-methyl group more acidic than the 4-methyl group, whereas in the parent bases, the 4-methyl group was more acidic than the 2-methyl group.

Table IV. Pseudo-First-Order Reaction Rate Constants for the Hydrogen-Deuterium Exchange Reaction of the Methyl Groups of Dimethylazines and Their N-Oxides (sec^{-1})



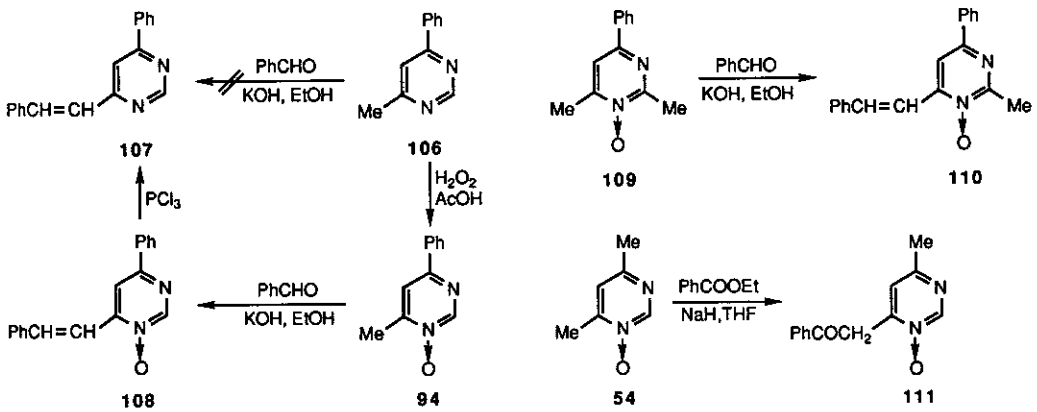
4-Me: 6.4×10^{-5} NaOD: 5%, 100°C	4-Me: 12×10^{-5} NaOD: 5%, 50°C	4-Me: 9.1×10^{-5} NaOD: 1%, 20°C	4-Me: 1.4×10^{-4} NaOD: 1%, 50°C	4-Me: 1.1×10^{-4} NaOD: 1%, 50°C



2-Me: 1.8×10^{-4} NaOD: 1%, 50°C	2-Me: 8.4×10^{-4} NaOD: 1%, 20°C	2-Me: 8.1×10^{-4} NaOD: 0.1%, 20°C	3-Me: 7.9×10^{-4} NaOD: 1%, 20°C	6-Me: 1.9×10^{-4} NaOD: 1%, 20°C

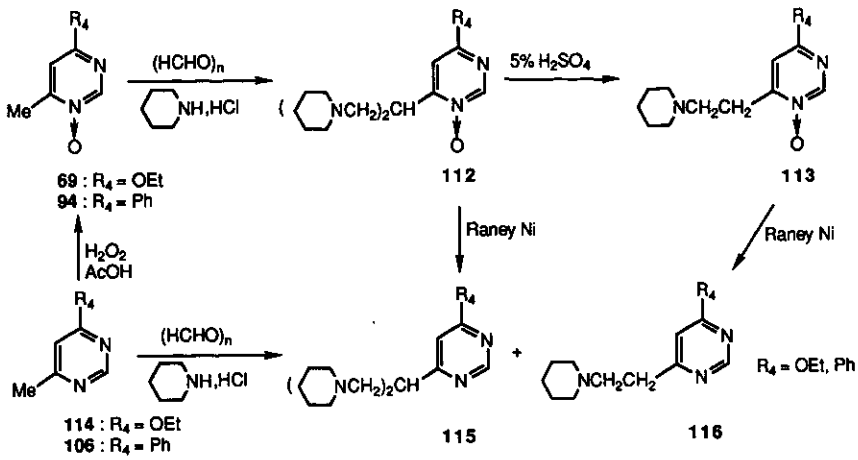
It is well known that 6-methyl-4-phenylpyrimidine (**106**) reacts with benzaldehyde in the presence of zinc chloride to give 4-phenyl-6-styrylpyrimidine (**107**)[107] although

this condensation did not proceed in the presence of ethanolic potassium hydroxide. In contrast, the condensation of 6-methyl-4-phenylpyrimidine 1-oxide (**94**) with benzaldehyde was effectively promoted by ethanolic potassium hydroxide at room temperature, and 4-phenyl-6-styrylpyrimidine 1-oxide (**108**) was obtained in good yield.[107] When 2,6-dimethyl-4-phenylpyimidine 1-oxide (**109**) was treated with an equivalent amount of benzaldehyde, 2-methyl-4-phenyl-6-styrylpyrimidine 1-oxide (**110**) was obtained selectively. 4,6-Dimethylpyrimidine 1-oxide (**54**) was site-selectively benzoylated with ethyl benzoate under basic conditions to give 6-benzoylmethyl-4-methylpyrimidine 1-oxide (**111**).[106] These results are actual evidence for the activating effect of an N-oxide group on a neighboring methyl group during an aldol-type condensation.



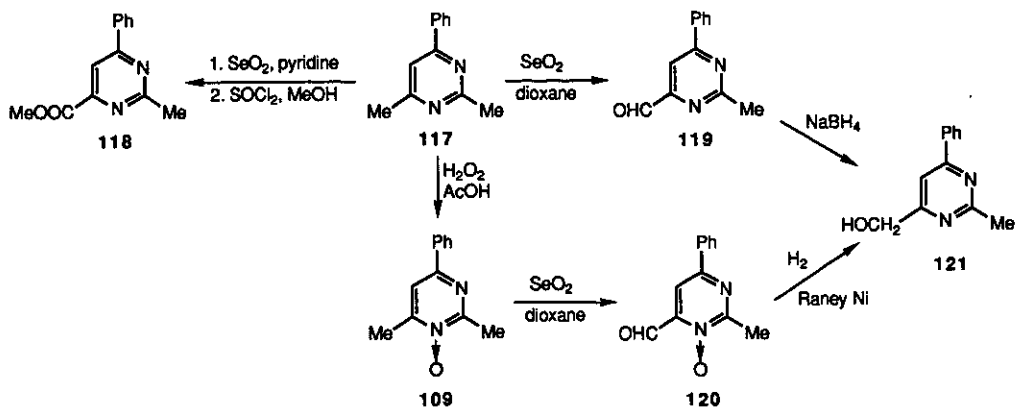
Scheme 40

There is only one example involving the Mannich reaction[107] of methylpyrimidine N-oxides. Thus, 4-ethoxy-6-methyl- (**69**) and 6-methyl-4-phenylpyrimidine 1-oxide (**94**) both reacted with formaldehyde and piperidine to give the corresponding bis(piperidinomethyl) compounds (**112**) which were converted into the piperidino-ethylpyrimidine N-oxides (**113**) by treatment with sulfuric acid. When 4-ethoxy-6-methyl- (**114**) and 4-methyl-6-phenylpyrimidine (**106**) were separately treated under the same conditions, a mixture of the corresponding bis(piperidinomethyl) (**115**) and the piperidinoethyl derivatives (**116**) was obtained, but it proved difficutl to separate them. The introduction of an N-oxide group into the pyrimidine ring is apparently favorable in giving each bis(piperidinomethyl)pyrimidines as the single product.



Scheme 41

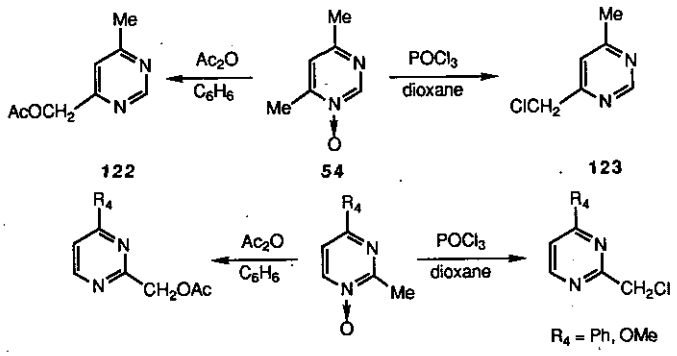
The bromination of 6-methyl-4-phenylpyrimidine 1-oxide with bromine in acetic acid has been reported.[26] Although the dibromomethyl compounds thus obtained, were convertible into aldoximes,[36] the formation of too many products removed any real synthetic significance from the bromination reaction (see Section VI,A, Scheme 38). 2,4-Dimethylpyrimidines were oxidized with selenium dioxide in dioxane to give the corresponding pyrimidine-4-carboxaldehydes,[108] and in pyridine to give the 4-carboxylic acids.[109] 2,6-Dimethyl-4-phenylpyrimidine 1-oxide (**109**) reacted more rapidly with selenium dioxide in dioxane to give the pyrimidine-6-carboxaldehyde 1-oxides (**120**)[108] (see Section III,C). The reduction of the pyrimidine-carboxaldehydes (**119,120**) with sodium borohydride or catalytic hydrogenation over Raney nickel gave the same pyrimidine-4-methanol (**121**).



Scheme 42

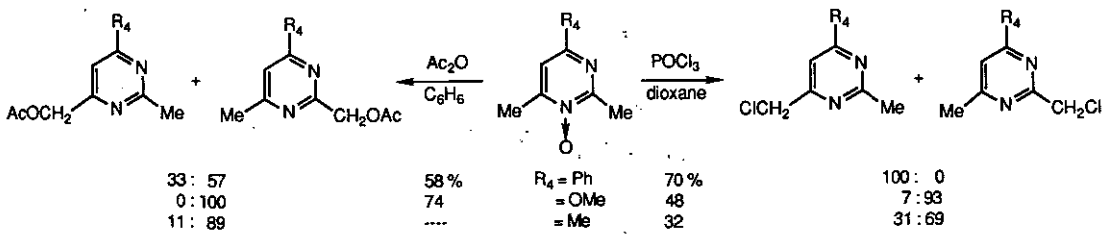
C. Reactions between an N-Oxide Group and a Neiboring Active Methyl Group

2- or 4-Methylpyrimidine N-oxides undergo the deoxygenative acetoxylation upon treatment with acetic anhydride to give principally the corresponding acetoxymethylpyridines.[110] Similarly, the reaction with acid chlorides affords mainly the chloromethylpyridines.[111] Initially, a poor formation of 4-acetoxymethyl-6-methyl- (**122**) and 4-chloromethyl-6-methylpyrimidine (**123**) was reported[20] for the reaction of 4,6-dimethylpyrimidine 1-oxide (**54**) with neat acetic anhydride and tosyl chloride respectively. Subsequently, these reactions were modified and proved successful with various methylpyrimidine N-oxides under mild conditions. Thus, dilution of acetic anhydride with benzene[112] and the use of phosphoryl chloride in dioxane[113] gave much better results. Unlike the reaction of methylpyridine N-oxides, any ring substitution products were not formed in the pyrimidine series.



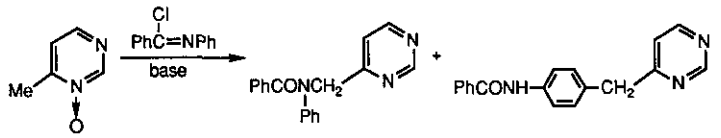
Scheme 43

Furthermore, when 4-substituted 2,6-dimethylpyrimidine 1-oxides were employed, both *reactions were affected by the nature of the 4-substituent and consequent* synthetically significant site-selectivity was observed.[15,112]



Scheme 44

The reaction of 2-methylquinoline 1-oxide with benzoyl chloride in the presence of sodium hydroxide[114,115] and the reaction with sodium p-toluenesulfinate and tosyl cyanide[114] have been reported to give 2-(benzoylmethyl)- and 2-(tosylmethyl)-quinoline, respectively. Such side-chain reactions have not been investigated extensively, but the reaction of 6-methylpyrimidine 1-oxide (5) with α-chloro-benzylideneaniline under basic conditiones has been reported[117] to give a benzoylaminomethylpyrimidine (**124**) as the main product together with the benzylpyrimidine (**125**).

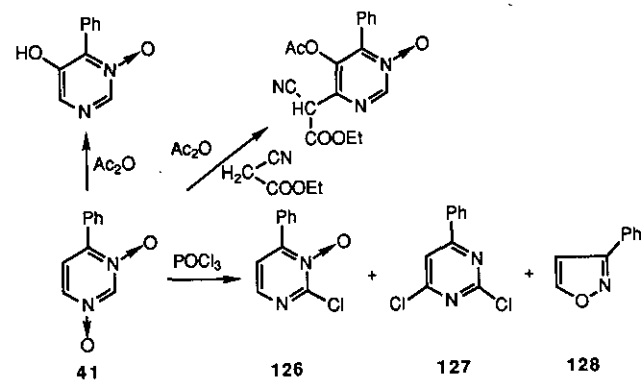


5 **124** **125**

Scheme 45

IX. REACTIONS OF PYRIMIDINE DI-N-OXIDES

When pyrimidine di-N-oxides were treated by methods conventionally employed in mono-N-oxide chemistry, normal results were observed. For example, in the reaction of 4-phenylpyrimidine 1,3-dioxide (**41**) with phosphoryl chloride, 2-chloro-6-phenyl-pyrimidine 1-oxide (**128**) was isolated as the main product accompanied by small amounts of 2,4-dichloro-6-phenylpyrimidine (**127**) and 3-phenylisoxazole (**128**).[49] Other examples[118] in this category are illustrated in Scheme 46.

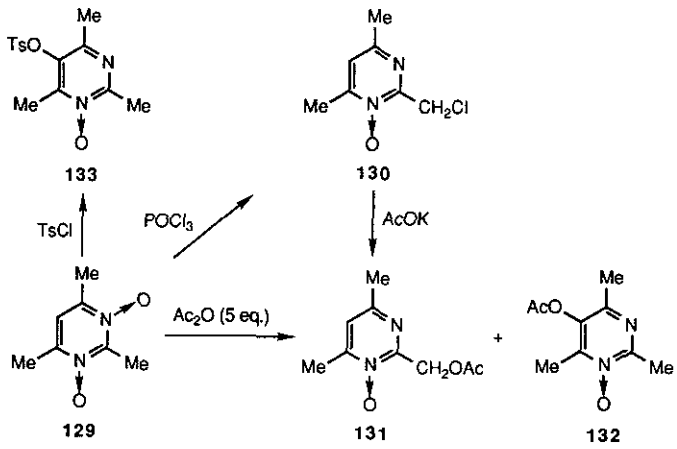


41 **126** **127** **128**

Scheme 46

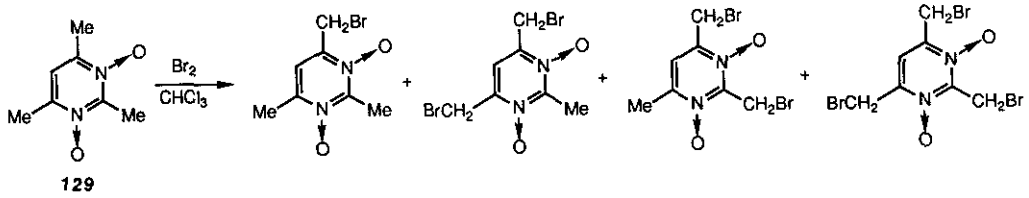
The reaction of 2,4,6-trimethylpyrimidine 1,3-dioxide (**129**) with phosphoryl chloride, like that of the corresponding mono-N-oxide, gave the 2-chloromethyl-pyrimidine 1-oxide (**130**).[50] On the other hand, the reaction with acetic anhydride yielded a mixture of the 2-acetoxymethyl 1-oxide (**131**) and the 5-acetoxy 1-oxide

(**132**) while the reaction with tosyl chloride afforded the 5-tosyloxy derivative (**133**) exclusively.[50]



Scheme 47

As shown below, 2,4,6-trimethylpyrimidine 1,3-dioxide (**129**) is susceptible to side-chain bromination,[50] but it is of little synthetic value because of the formation of many products.

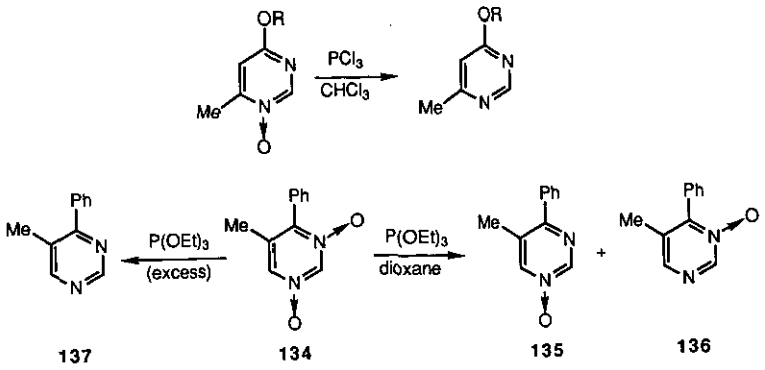


Scheme 48

X. DEOXYGENATION OF AN N-OXIDE GROUP

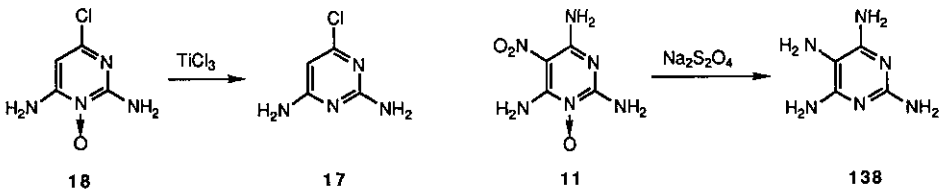
Like pyridine and quinoline N-oxides, pyrimidine N-oxides are reduced to the corresponding parent bases by treatment with trivalent phosphorus compounds: phosphorus trichloride is the most practical and the yields of the parent bases are satisfactory in general.[23,24,104] *Triethyl phosphite has also been employed to* deoxygenate pyrimidine N-oxides.[26]

When 5-methyl-4-phenylpyrimidine 1,3-dioxides (**134**) were treated with triethyl phosphite in dioxane, a mixture of the 1-oxide (**135**) and the 3-oxide (**136**) was obtained, while the reaction with excess triethyl phosphite alone at 160°C resulted in the deoxygenation of both N-oxide groups.[47,48]



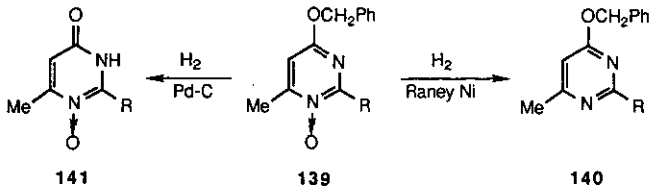
Scheme 49

Titanium trichloride has also been reported as a favorable reagent for removing an oxygen atom from 2,6-diamino-4-chloropyrimidine 1-oxides (**18**).[119] It should be mentioned that the 4-chloro substituent remained intact during this reduction. In contrast, the catalytic hydrogenation of 4-chloro-6-methylpyrimidine 1-oxide over palladium-charcoal gave 6-methylpyrimidine 1-oxide selectively[58] (see Section VIII,A, Scheme 38). Sodium dithionite reduced 2,4,6-triamino-5-nitropyrimidine 1-oxide (**11**) to 2,4,5,6-tetraminopyrimidine (**138**).[4]



Scheme 50

The behavior of heteroaromatic N-oxides in catalytic hydrogenation seems to be affected strongly by the nature of the catalyst employed. The hydrogenation of the 4-benzyloxypyrimidine 1-oxides (**139**) is a typical example. Thus **139** were hydrogenated over Raney nickel to give the 4-benzyloxypyrimidines (**140**), whereas the reduction over palladium-charcoal afforded the 4-pyrimidinone 1-oxides (**141**).[120]



Scheme 51

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27. When 4-phenoxyquinazoline was treated with 30% H_2O_2 in acetic acid, the 4-phenoxyl group was hydrolyzed completely[127] to give 4(3H)-quinazolinone. 4-Phenoxyquinazoline 1-oxide was prepared by the oxidation with monoperphthalic acid in ether.[128] This is a typical example showing the easy bond fission of the 4-phenoxyl group at the pyrimidine ring. Accordingly, it remains necessary to reinvestigate the N-oxidation of 2,6-dimethyl-4-phenoxypyrimidine with H_2O_2 in acetic acid, because a 75% recovery of the 4-phenoxypyrimidine has been reported.[22]

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