CONVERSION OF SIMPLE PYRIMIDINES INTO DERIVATIVES WITH A CARBON FUNCTIONAL GROUP#

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Abstract—— The synthesis of pyrimidine derivatives bearing carbon functional groups, such as CH_2OH, CHO, COR (or COAr), CN, $CONR_2$, and COOR, at the 2- or 4-position is described. The most practical and experimentally simplistic methods for the preparation of these pyrimidines are concluded to be as follows.

Hydroxymethylpyrimidines are best prepared by direct hydroxymethylation of pyrimidines with a free 2- or 4-position using hydroxymethyl radical. Pyrimidinealdehydes are readily obtained by oxidation of methylpyrimidines with a limited amount of selenium dioxide. It is recommended that acylpyrimidines are prepared from the corresponding nitriles by Grignard reaction. In some cases homolytic acylation, rather than the above method, can be used for their preparation.

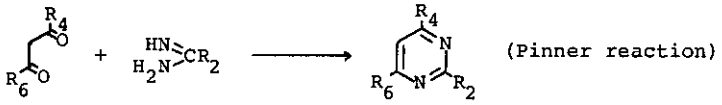
The synthesis of pyrimidinecarboxylic acids and related compounds is described together with the interconversion of nitriles, amides, and esters. In addition, selectivity of reactions on the pyrimidine ring occasionally observed during our investigations is discussed briefly in the last Chapter of this paper.

Contents

Dedicated to Professor Tetsuji Kametani, Pharmaceutical Institute, Tohoku University on the occasion of his retirement.

I INTRODUCTION

In 1848, Frankland and Kolbe carried out the first primary synthesis of a compound with a pyrimidine nucleous by the action of metallic potassium on propiononitrile.[1] Since then, a great many papers dealing with the synthesis of pyrimidine derivatives have been published. Most of this work until 1967, has been summerized in the text books of D. J. Brown,[2,3] which are the most reliable and convenient reviews of pyrimidine chemistry. According to these books, the most common synthesis of pyrimidines is exemplified by the condensation of β-diketones with alkylamidines to give 2,4,6-trialkylpyrimidines. Condensations of this type are named Pinner reactions.



(Pinner reaction)

In the condensation, one or both carbonyl groups of the three carbon fragment may be replaced by any other kind of equivalent carbonyl group, and the amidine may be replaced by urea, thiourea, and guanidine. Although a wide variety of pyrimidines can be prepared by this route, derivatives containing a carbon functional group attached directly to the ring other than the 5-position, are not readily accessible through this method. Accordingly, pyrimidines with CH_2OH, CHO, COR, CN, and COOR groups at the 2- or 4-(6-) position formed a relatively little explored family until the first half of 1970's.

From this point of view, our interest was focussed on the introduction of such groups into the pyrimidine ring by methods with experimental simplicity and wide applicability. After preliminary work, we reached the conclusion that the conversion of simple pyrimidines, easily obtained by the common synthesis, to the desired compounds was more convenient than direct synthesis by ring-closure reaction of open-chain materials having appropriately protected substituents. In the present paper, we wish to outline our recent work on the reactions of simple pyrimidines, in comparison with traditional methods reported in the literature.

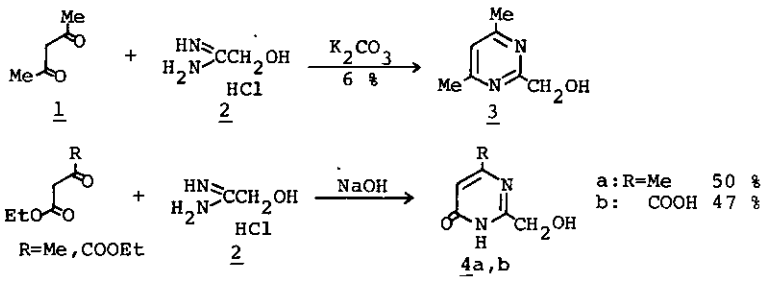
II SYNTHESIS OF HYDROXYMETHYLPYRIMIDINES

II-a By Traditional Methods

Few pyrimidines with a hydroxymethyl group on the 2- or 4-position were known prior to our work. Brown et al.[4] reported the condensation of acetylacetone (1) and hydroxyacetamidine (2), but the yield of the desired product, 4,6-dimethylpyrimidine-2-methanol (3), was less than 10 %. However, condensation of ethyl acetoacetate with 2 was reported to give 2-hydroxymethyl-6-methyl-4-pyrimidinone (4a) in 50 % yield.[5] In our experience,[6] the condensation of ethyl acetoacetate with

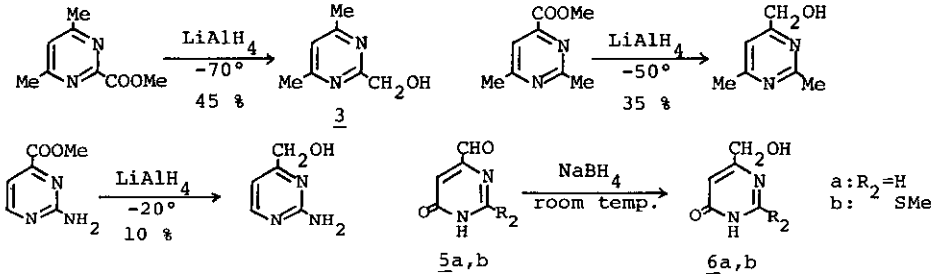
an amidine usually proceeds better than that of acetylacetone with the same amidine.

The direct synthesis of 4-hydroxymethylpyrimidines has not yet been reported, probably due to difficulty in synthesis of the starting materials.



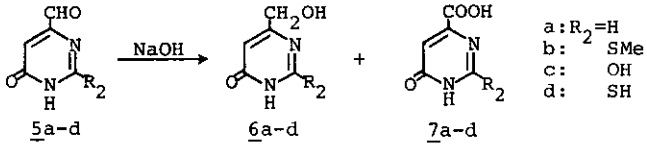
Scheme 1

Reductions of pyrimidine esters or aldehydes with lithium aluminum hydride[4,7] or sodium borohydride[8] were reported to give the corresponding hydroxymethyl compounds. Although examples of these reactions are illustrated in Scheme 2, they are not of wide application. Since the restriction on the preparation of the starting materials, the esters and aldehydes, has been removed as described in Chapters III and IV, the above reductions may gradually become more popular for the preparation of hydroxymethylpyrimidines.



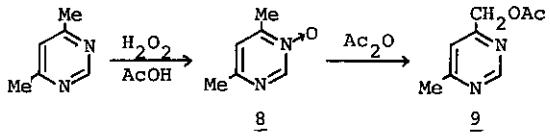
Scheme 2

The Cannizzaro reaction of 6-formyl-4-pyrimidinones (5) was reported to give 6-hydroxymethyl-4-pyrimidinones (6) together with the corresponding carboxylic acids (7)[8,9] The poor availability of pyrimidinealdehydes also restricted the development of reactions of this type.



Scheme 3

Furthermore, the reaction of 4,6-dimethylpyrimidine N-oxide (8) with acetic anhydride was reported to give a small amount of 4-acetoxymethyl-6-methylpyrimidine (9),[10] although the reaction of 2-methylpyridine N-oxide with the same reagent is known to give 2-acetoxymethylpyridine in considerable yield.[11-13] In our experience,[6] pyrimidine N-oxides with an α-methyl group usually gave resinous products when they are heated in acetic anhydride.



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Scheme 4

II-b By Homolytic Substitution

Recently, Minisci and co-workers developed a new homolytic carbon-carbon bond formation on N-heteroaromatics by means of functionized radicals generated by the oxidation of appropriate aliphatic compounds.[14-23] The reported procedures for the generation of these radicals are briefly represented as follows.

Method A: MeOH + $(NH_4)_2S_2O_8$ (for hydroxymethylation by $\dot{C}H_2OH$)[14]

Method B: RCOCOOH + $(NH_4)_2S_2O_8$ + $AgNO_3$ (for acylation by $\dot{C}OR$)[18,19]

Method C: RCHO + t-BuOOH + $FeSO_4$ (for acylation by $\dot{C}OR$)[15-19]

Method D: R'RNCHO + t-BuOOH + $FeSO_4$ (for amidation by $\dot{C}ONRR'$)[20-22]

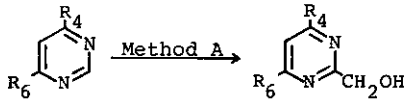
Method E: MeCOCOOEt + H_2O_2 + $FeSO_4$ (for ethoxycarbonylation by $\dot{C}OOEt$)[23]

They have advocated that, unlike a phenyl radical, the radicals generated by the above methods selectively attack the electron-defficient positions of pyridine, quinoline, and isoquinoline rings. Since pyrimidines are recognized to be rather more electron-defficient than the corresponding pyridines, application of Method A-E was expected to be effective for the preparation of pyrimidine derivatives.

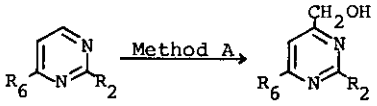
Firstly, hydroxymethylation according to Method A was employed for the synthesis of 2- or 4-hydroxymethylpyrimidines.[24,25] When 4,6-dimethylpyrimidine was treated with ammonium peroxydisulfate and sulfuric acid in methanol, 4,6-dimethylpyrimidine-2-methanol (3) was obtained in excellent yield as expected. Similarly, 2-isopropyl-6-methylpyrimidine was converted to 2-isopropyl-6-methylpyrimidine-4-methanol under almost identical conditions.[25] In both cases, contamination of the product by the 5-positional isomers or the dihydroxymethyl compounds was not observed.

The results obtained from hydroxymethylation of several pyrimidines are listed

in Scheme 5. Based on these data, the application of Minisci's method seems to be, at present, the best way to prepare such carbinols.



R_4	R_6			
Me	Me	93 %	mp	87-88°
Me	Ph	48	bp	149-150°(1 mmHg)
Me	OMe	42	mp	56.5-57°



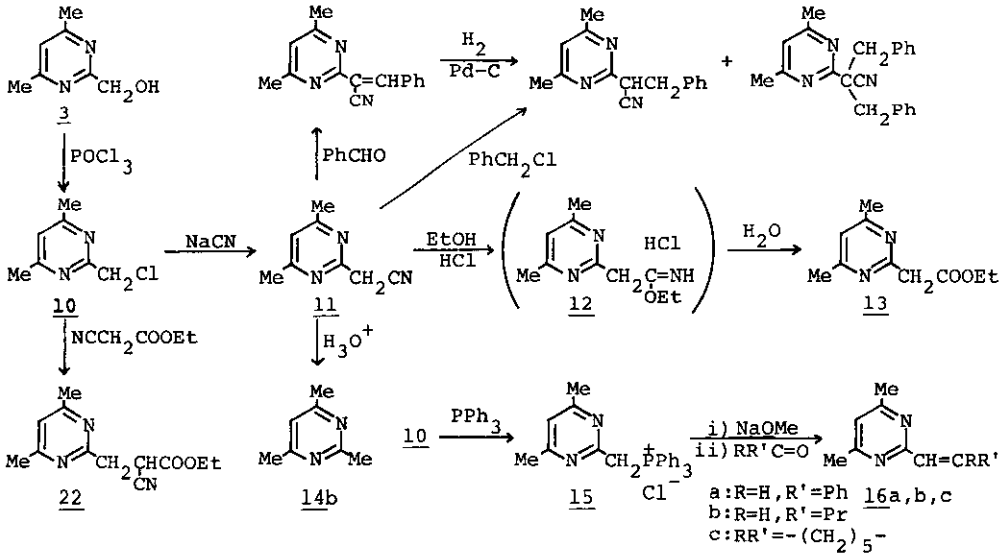
R_2	R_6			
Me	Me	50 %	mp	108.5-110°
i-Pr	Me	53	bp	135-138°(20 mmHg)
Me	Ph	65	mp	95-96°
Ph	Me	64	bp	151-152°(1 mmHg)
Me	OMe	43	mp	116-116.5°
OMe	Me	28	mp	146-147°

Scheme 5

II-c Synthetic Utility of Hydroxymethylpyrimidines

As already mentioned, the preparation of the title compounds with simple alkyl (or aryl) substituents had been little investigated. Thus the chemical properties of hydroxymethylpyrimidines, as possible synthetic intermediates, were investigated at this time.[25]

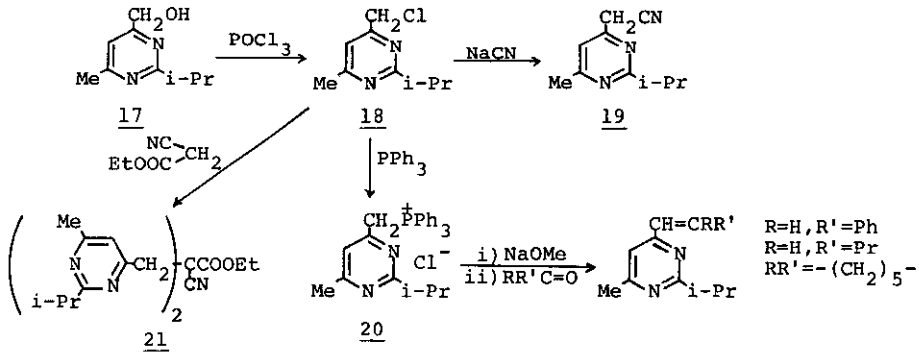
When 3 was heated with phosphoryl chloride in chloroform, 2-chloromethyl-4,6-dimethylpyrimidine (10) was obtained as a colorless solid, while the reaction of 3 with thionyl chloride failed to give any significant product. Upon heating 10 with sodium cyanide in aqueous methanol, 4,6-dimethylpyrimidine-2-acetonitrile (11) was obtained. Although the direct hydrolysis of 11 with dilute hydrochloric acid brought about decarboxylation to give 2,4,6-trimethylpyrimidine (14b), ethyl 4,6-



Scheme 6

dimethylpyrimidine-2-acetate (13) was obtained by ethanolysis of 11 via the corresponding ethyl imidate (12). The synthesis of the 2-alkenyl derivatives (16) through the Wittig reaction of the phosphonium salts (15) may supplement the defect on the condensation of polymethylpyrimidines and aldehydes. Namely, as described later, the Knoevenagel reaction of 14b with benzaldehyde is known to occur at the 4-methyl group predominantly, so that the selective preparation of 4,6-dimethyl-2-styrylpyrimidine (16a) is difficult. Other reactions which have been carried out are shown in Scheme 6.[25]

Similarly, the 4-methanol (17) was converted into the 4-chloromethylpyrimidine (18). This product (18) is stable enough to be a useful synthetic intermediate. The reaction of 18 with sodium cyanide or triphenylphosphine gave the expected products (19,20).[25]



Scheme 7

When 18 was treated with ethyl cyanoacetate under basic conditions, the bispyrimidinylmethyl compound (21) was obtained instead of the compound corresponding to the normal product (22) from 10.[25]

III SYNTHESIS OF PYRIMIDINEALDEHYDES

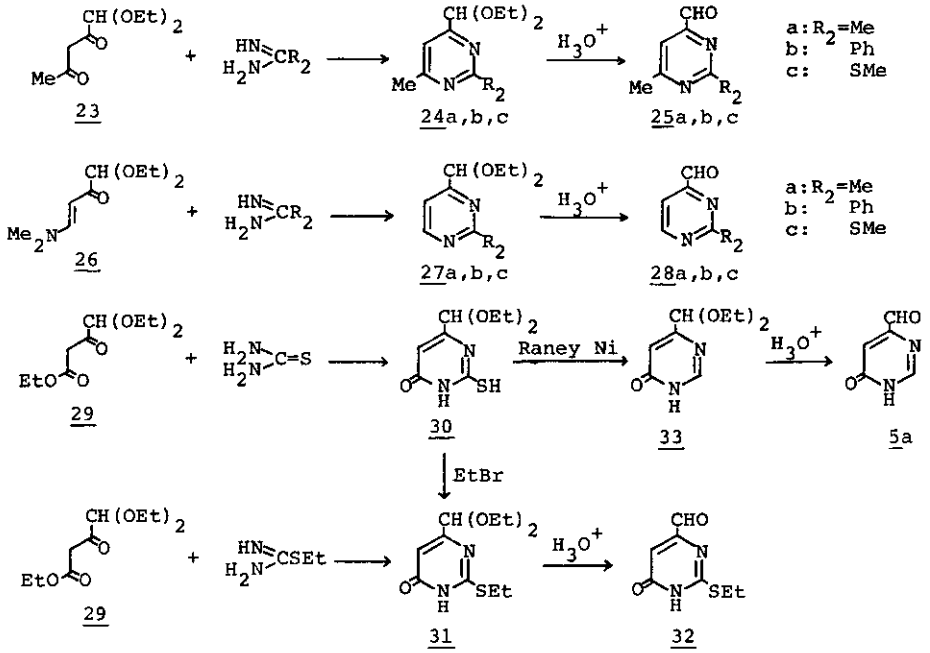
III-a By Ring-Closure Reaction

Although free aldehydes cannot be made by the Pinner-type ring closure reaction, pyrimidines with a dialkoxymethyl group can be prepared in this way. For example, the condensation of γ,γ-diethoxyacetylacetone (23) or the enaminoketone (26) with alkylamidines leads to the 4-diethoxymethylpyrimidines (24,27),[26] which are hydrolized to give free aldehydes (25,28). Like amidines, S-methylthiourea readily reacted with 23 and 26 to give 24c and 27c respectively. Desulfurization of 24c and 27c was also known to give the derivatives with the free 2-position.[26]

Similarly, it was reported that condensation of ethyl γ,γ-diethoxyacetoacetate

(29) with thiourea, followed by alkylation with ethyl bromide gave 6-diethoxymethyl-2-ethylthio-4-pyrimidinone (31)[28] which was also prepared by reaction of 29 with S-ethylpseudothiourea.[32] Raney nickel desulfurization of the acetal (30) afforded 6-diethoxymethyl-4-pyrimidinone (33) without any difficulty.[29] The removal of the protecting group from both acetals (31,33) gave rise to the free aldehydes (32,5a), whose Cannizzaro reaction was mentioned in Section II-a.

Although several pyrimidine-4-aldehydes have been synthesized in this way,[26-32] no report has appeared in the literature regarding the synthesis of pyrimidine-2-aldehydes by similar ring-closure reaction.



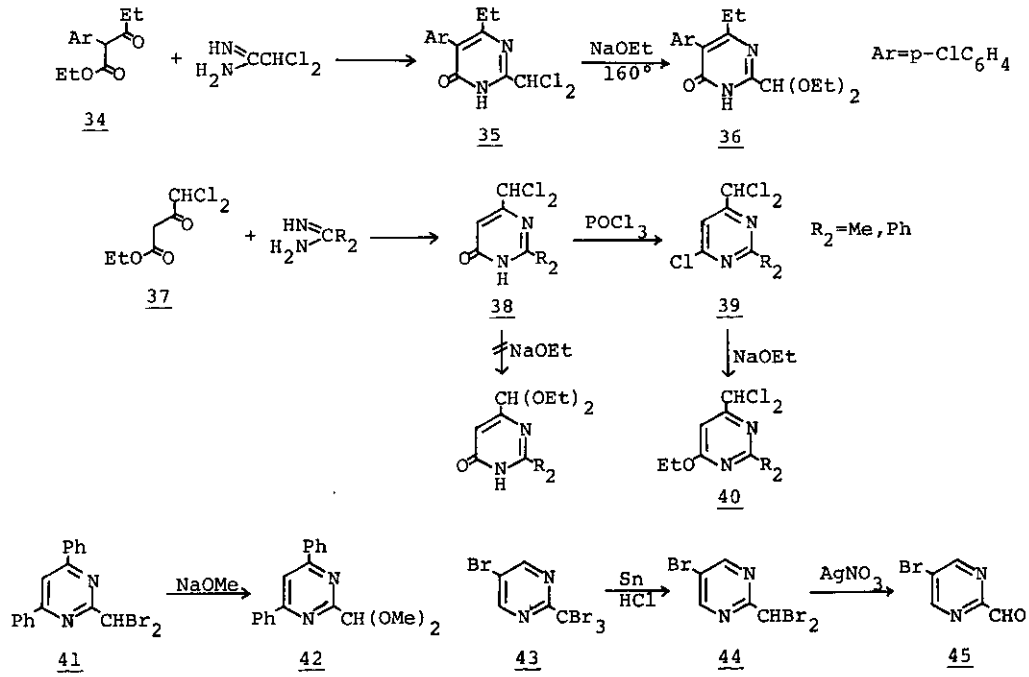
Scheme 8

A dichloromethyl group at the 2-position was known to be convertible to a dialkoxymethyl group by treatment with sodium alkoxides, although somewhat drastic conditions seem to be necessary.[33] Namely, dichloroacetamidine reacted with ethyl α-p-chlorophenylpropionylacetate (34) to give 5-p-chlorophenyl-2-dichloromethyl-6-ethyl-4-pyrimidinone (35), which was transformed into the corresponding acetal (36) by the action of sodium ethoxide in ethanol at 160° in a sealed tube.

6-Dichloromethyl-4-pyrimidinones (38), which were synthesized by the Pinner reaction of ethyl γ,γ-dichloroacetoacetate (37) with amidines, were recovered when they were treated with sodium ethoxide in boiling ethanol under atmospheric pres-

sure.[6] Similarly, the reaction of 39 with sodium ethoxide under comparable conditions gave 40 in which the 4-dichloromethyl group is still intact. On the other hand, Mamaev et al. obtained 2-dimethoxymethyl-4,6-diphenylpyrimidine (42) from the corresponding 2-dibromomethyl compound (41) on treatment with sodium methoxide.[34]

The direct conversion of a dibromomethyl group into an aldehyde group was also reported.[35] Namely, 5-bromo-2-dibromomethylpyrimidine (44) prepared from 5-bromo-2-tribromomethylpyrimidine (43), reacted with silver nitrate to give 5-bromopyrimidine-2-carboxaldehyde (45). Accordingly, treatment of dihalomethylpyrimidines under appropriate conditions, may be regarded as one method for the preparation of pyrimidinealdehydes.



Scheme 9

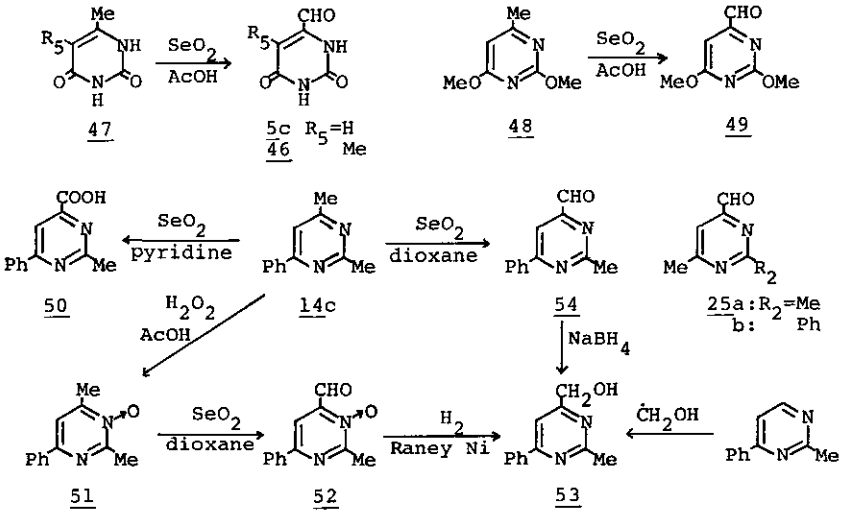
III-b Oxidation of Methyl Group with Selenium Dioxide

The oxidation of a methyl group with selenium dioxide is a standard method for the preparation of N-heteroaromatic aldehydes. It is surprising that such a simple reaction had been little applied to the preparation of pyrimidinealdehydes, other than 5c, 46, and 49.[36,37] Recently we attempted the oxidation of polymethylpyrimidines with a limited amount of selenium dioxide in dioxane, and found the 4-methyl group to be site-selectively oxidized to an aldehyde group.[38] For example, the oxidation of 2,4-dimethyl-6-phenylpyrimidine (14c) afforded 2-methyl-6-phenylpyri-

midine-4-carboxaldehyde (54) as the sole product. The introduction of an N-oxide group makes this oxidation easier; e.g. 2,4-dimethyl-6-phenylpyrimidine 3-oxide (51) was transformed into the aldehyde N-oxide (52) within 2 hr., whereas the oxidation of 14c under identical conditions required a reaction time of 4-5 hr.[38]

The reduction of 54 with sodium borohydride and the catalytic reduction of 52 afforded the same and known carbinol (53), demonstrating the location of the aldehyde group. Similar results were obtained on the oxidation of 2,4,6-trimethylpyrimidine (14b) and 4,6-dimethyl-2-phenylpyrimidine, giving the 4-aldehydes (25a,b) as main products.

The use of pyridine instead of dioxane as solvent caused further oxidation of the product.[85] For example, the oxidation of 14c in pyridine gave 2-methyl-6-phenylpyrimidine-4-carboxylic acid (50) selectively. This oxidation is described further in Chapter V.



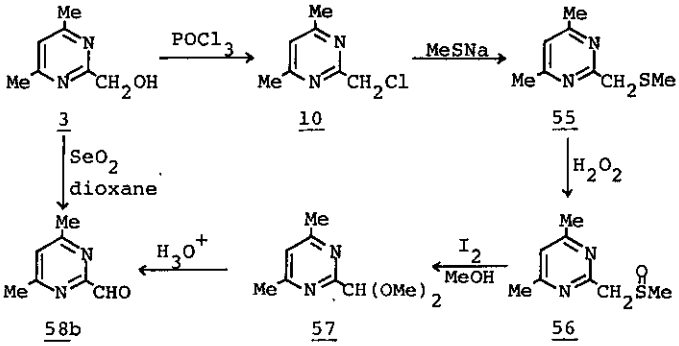
Scheme 10

The preparation of pyrimidinealdehydes in the above way is straightforward, although there is one restriction on its application. The 2-methyl groups are never selectively oxidized when a 4-methyl group is present in the same molecule. Oxidation of 2-hydroxymethylpyrimidines with the same reagent should be evaluated for the synthesis of the 2-aldehydes.

III-c By Other Oxidative Process

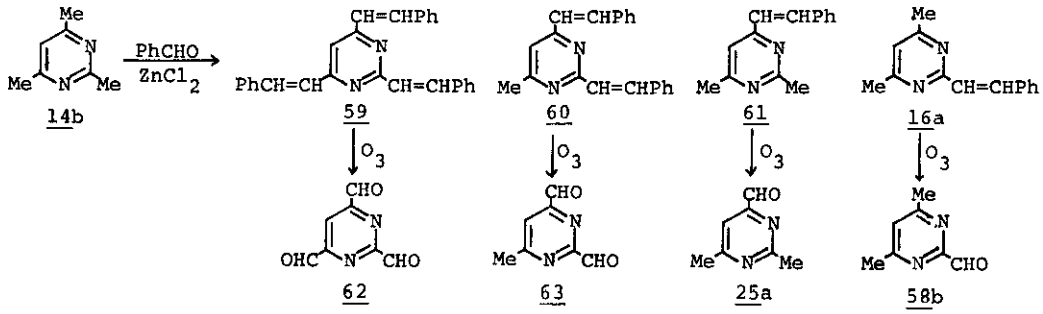
2-Chloromethyl-4,6-dimethylpyrimidine (10), obtained by dehydroxychlorination of 3 with phosphoryl chloride, was readily converted into the sulfoxide (56) via

4,6-dimethyl-2-methylthiomethylpyrimidine (55). The Pummerer reaction of 56 with iodine in methanol gave 2-dimethoxymethyl-4,6-dimethylpyrimidine (57) which was converted to 4,6-dimethylpyrimidine-2-carboxaldehyde (58b). Although the direct oxidation of 3 with a limited amount of selenium dioxide in dioxane gave the same aldehyde (58b) in considerable yield, the transformation of a 2-hydroxymethyl group into a formyl group by the Pummerer reaction may be utilized alternatively in some cases.[25]



Scheme 11

Ozonization of styrylpyrimidines followed by catalytic reduction has not been well investigated. The condensation of 14b with excess benzaldehyde in the presence of zinc chloride gave 2,4,6-tristyrylpyrimidine (59),[39,42] while the reaction with less benzaldehyde afforded dimethyl-styrylpyrimidine or distyryl-methylpyrimidine mainly, depending on the amount of benzaldehyde used.[39,40] The ozonolysis of 59, 2,4-distyryl-6-methyl- (60), and 4,6-dimethyl-2-styryl-pyrimidine (16a) thus obtained was reported to give the corresponding tri- (62), di- (63), and mono-aldehyde (58b). Since the structure 16a was revised later to be 2,6-dimethy-4-styryl-pyrimidine (61),[41] this aldehyde (58b) is likely to be the 4-aldehyde (25a).

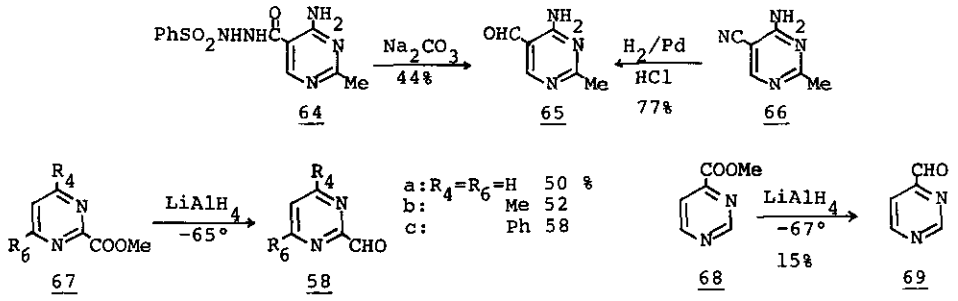


Scheme 12

Other examples of ozonolysis of styrylpyrimidines have not appeared in the literature. Since an alternative synthesis of styryl derivatives, by cross-coupling reaction of halopyrimidines with styrene, has been achieved with wide scope,[6] the preparation of pyrimidinealdehydes by ozonization should be reinvestigated systematically.

III-d By Other Means

The McFadyen-Stevens reduction of a pyrimidinecarboxylic acid[43] and the catalytic reduction of a cyanopyrimidine (66)[44] were reported for the preparation of the 5-aldehyde (65), but application of these reactions to the synthesis of 2- and 4-isomers has been not reported. Careful reduction of methyl pyrimidine-2-carboxylates (67) with lithium aluminum hydride was investigated by Mamaev et al.[45] and the corresponding 2-aldehydes (58) were obtained in moderate yield. Although the reduction of methyl pyrimidine-4-carboxylate (68) was also reported to give 69,[46] this reduction seems not to have any value as a preparative route.

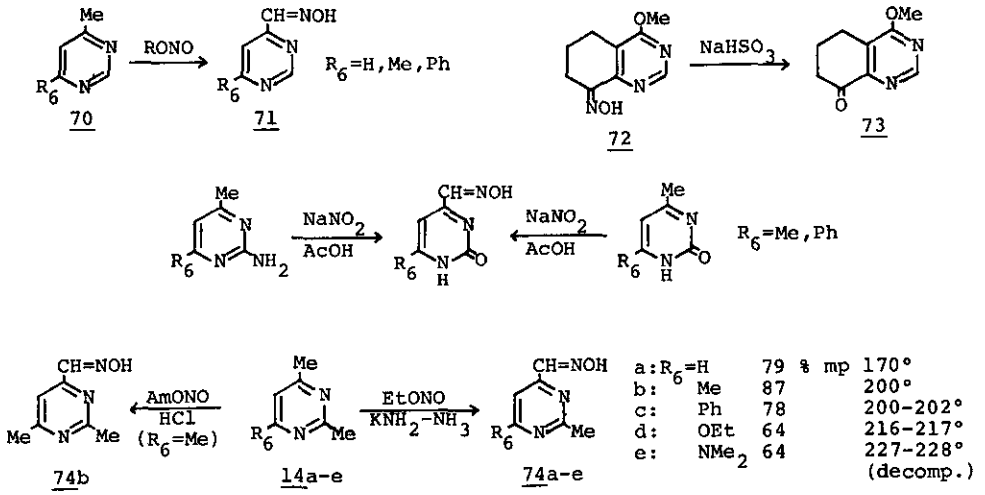


Scheme 13

Nucleophilic substitution on 2- or 4-chloropyrimidines with compounds containing an active methylene (or methyl) group has not been well investigated. Accordingly, replacement of the active halogen atom with trithiane or FAMSO, to introduce aldehyde-equivalent substituents, still remains an unexplored field.

Methyl group attached to the active positions of pyrimidine ring are easily converted into the aldoxime group by nitrosation using appropriate nitrous acid derivatives under various conditions.[47-57] The presence of an electron-donating group does not retard the reaction.[57] Typical examples are illustrated in Scheme 14.

Since the aldoximes are obtained in satisfactory yield, it is regrettable that their transformation into the corresponding free aldehydes has not been successful. On the other hand, the ketone (73) was obtained from the ketoxime (72) by treatment with sodium bisulfite.[6] As described in Chapter V, this nitrosation should rather



Scheme 14

be evaluated as a practical procedure for the synthesis of 4-cyanopyrimidines.

Interestingly, nitrosation occurred selectively at the 4-methyl group in a 2,4-dimethylpyrimidine. Various 6-substituted 2,4-dimethylpyrimidines (14a-e) were reported to react with ethyl nitrite in liquid ammonia in the presence of potassium amide to give the aldoximes (74a-e) as sole products.[55-57] This selectivity was also observed under acidic conditions, e.g. 2,6-dimethylpyrimidine-4-aldoxime (74b) was obtained from the reaction of 14b with amyl nitrite in ethanolic hydrogen chloride.[54]

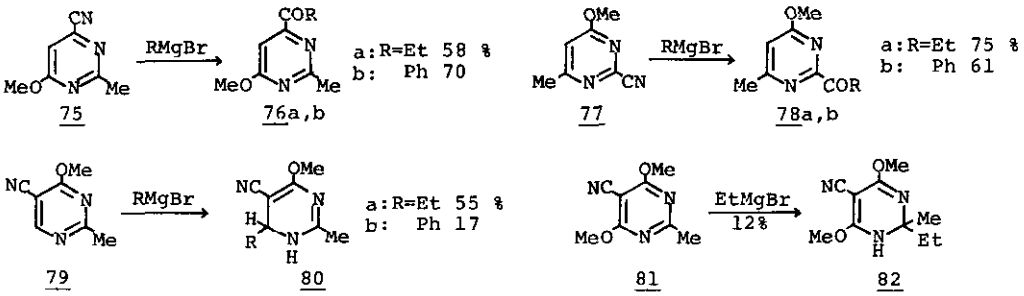
IV SYNTHESIS OF PYRIMIDINYL KETONES

IV-a By the Grignard Reaction

As well as general aromatic nitriles, 2- and 4-cyanopyrimidines smoothly react with a variety of Grignard reagents to give the corresponding ketones.[58] For example, the Grignard reaction of 6-methoxy-2-methylpyrimidine-4-carbonitrile (75) with ethylmagnesium bromide gave the 4-propionylpyrimidine (76a) in good yield. Similarly the 2-cyano derivative (77) was converted into 2-acyl-4-methoxy-6-methylpyrimidines (78a,b) as expected.

It is worth pointing out that the reaction of 5-cyanopyrimidines with Grignard reagents generally proceeds to give compounds with dihydropyrimidine skeletons instead of the expected ketones.[58] Typical examples (*79*⟶*80*, *81*⟶*82*) are illustrated in Scheme 15.

Since Grignard reaction on 2- and 4-cyanopyrimidines is an experimentally simplistic procedure, the facile preparation of these nitriles is considered to be the



75 76a,b 77 78a,b 79 80 81 82

Scheme 15

key to the successful synthesis of pyrimidinyl ketones.

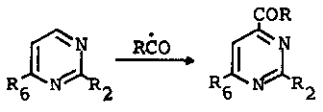
IV-b By Direct Homolytic Acylation

As briefly mentioned before, Minisci and co-workers[15-19] reported the generation of acyl radicals by the following two procedures (Methods B and C).

Method B: $RCOCOOH + (NH_4)_2S_2O_8 + AgNO_3$

Method C: $RCHO + t\text{-}BuOOH + FeSO_4$

These acyl radicals were expected to be nice species for the preparation of pyrimidinyl ketones, because good results were reported on the acylation of pyridine and quinoline derivatives. According to our experiments, the radicals generated by the above methods are concluded to have unfavorable character for the preparation of 2-pyrimidinyl ketones, although they are widely utilized in the preparation of 4-pyrimidinyl ketones.[59] Although the yields of 4-acetyl-2-methyl-6-phenylpyrimidine from 2-methyl-6-phenylpyrimidine by Methods B and C were comparable, Method C seems to have wider applicability because aldehydes are, in general, more available than α-ketoacids.



R_2	R_6	R	Method B	Method C	mp or bp(mmHg)
Me	Me	Me	29%	—	96-98°(20)
Me	Ph	Me	52	75%	94-95.5°
Ph	Me	Me	64	—	82-83°
Me	Ph	Et	—	78	95-97°
Me	Ph	i-Pr	—	53	60-62°
Me	Ph	Ph	—	12	64-65.5°

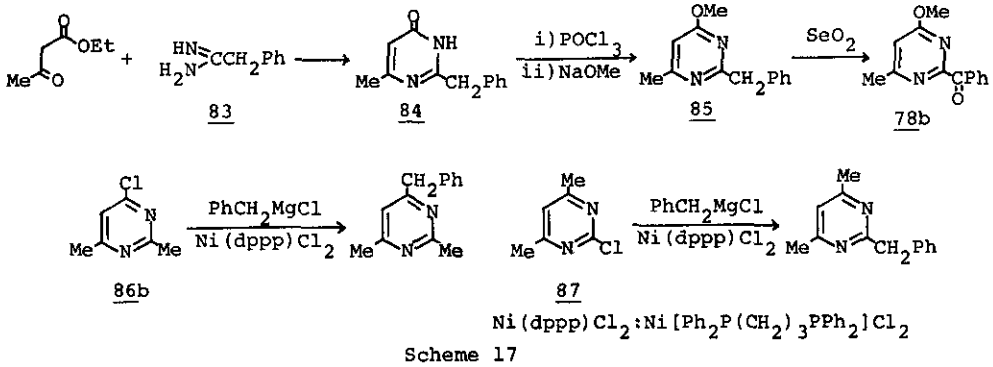
Scheme 16

As shown in Scheme 16, the acylation of simple pyrimidines with the free 4-position gave the products in satisfactory yield. Furthermore, less hydrophilic aldehydes gave lower yields of product, because aqueous conditions are required for the reaction. Based on the results shown in Scheme 16, it seems that direct benzoylation of simple pyrimidines in this way is unsuitable. The oxidation of benzylpyrimidines with selenium dioxide and the Grignard reaction of cyanopyrimi-

dines are recommended as alternative methods.[55]

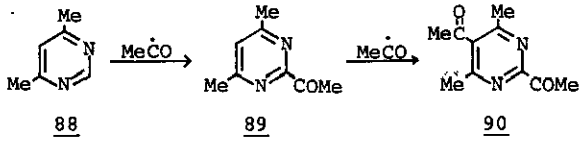
The Pinner reaction of ethyl acetoacetate with phenylacetamidine (83) gave 2-benzyl-6-methyl-4-pyrimidinone (84), which was converted into the 4-methoxypyrimidine (85) in the usual manner. Oxidation of 85 with selenium dioxide in ethanol afforded the benzoylpyrimidine (78b), with no accompanying oxidation of 6-methyl group. In general, 2- and 4-benzylpyrimidines are so conveniently synthesized by the cross-coupling reaction of 2- and 4-chloropyrimidines (86,87) with benzylmagnesium chloride, in the presence of a catalytic amount of nickel triphenylphosphine complex,[62] that oxidation of benzylpyrimidines to benzoylpyrimidines seems to be the best preparative route.

By the way, the discovery of the role of this nickel-triphenylphosphine complex, which facilitates remarkably the cross-coupling reaction of aryl halides with Grignard reagents, by Kumada et al.,[60,61] is doing a major service to heterocyclic chemistry. Most chloro derivatives of N-heteroaromatics are invariably obtained without experimental difficulty.



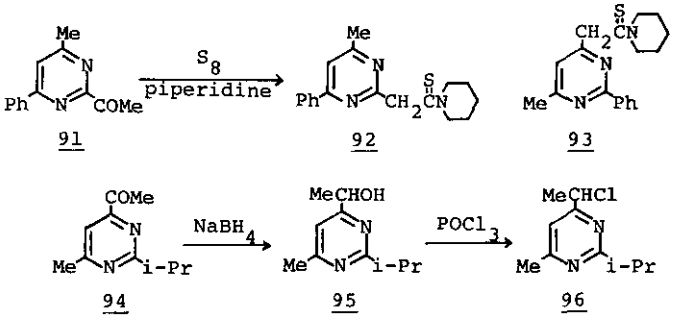
Scheme 17

On the other hand, when homolytic acylation was carried out on 4,6-dimethylpyrimidine (88) 2,5-diacetyl-4,6-dimethylpyrimidine (90) and 2-acetyl-4,6-dimethylpyrimidine (89) were obtained in comparable yields.[86] Since 89 was readily converted into 90 in higher yield, 89 is presumed to be an intermediate to 90. Based on the above findings, the preparation of 2-acylpyrimidines by homolytic acylation of pyrimidines in which the 2- and 5-positions are both free, seems to be unsuitable.



IV-c Reactions of Pyrimidinyl Ketones

No special features have yet been observed on the reactions of 2- and 4-pyrimidinyl ketones. For example, the Willgerodt-Kindler reaction of 2-acetyl-4-methyl-6-phenylpyrimidine (91) gave rise to the 2-thioacetamide (92).[6] The corresponding positional isomer (93) was obtained from 4-acetyl-6-methyl-2-phenylpyrimidine in the same manner. Sodium borohydride reduction of 4-acetyl-2-isopropyl-6-methylpyrimidine (94) proceeded to give the secondary alcohol (95) without ring reduction. Like the primary alcohol (17), the product (95) reacted with phosphoryl chloride to give the chloride (96).[6] On the basis of the above results, it is concluded that pyrimidinyl ketones behave like ordinary aromatic ketones.



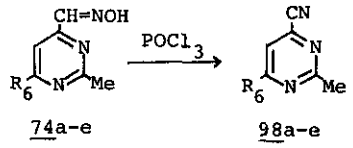
Scheme 18

V SYNTHESIS OF PYRIMIDINECARBOXYLIC ACIDS AND RELATED COMPOUNDS

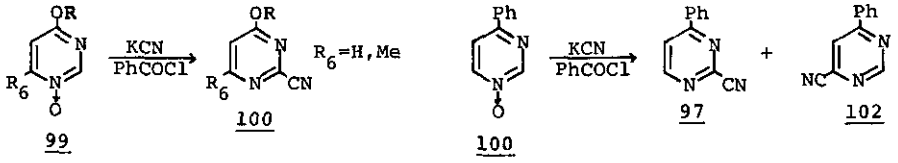
V-a Synthesis of Cyanopyrimidines

On treatment with phosphoryl chloride, pyrimidinealdoximes, obtained by the nitrosation of 4-methylpyrimidines, were converted into the corresponding nitriles.[51,52,55-57] However , the preparation of 2-cyanopyrimidines from 2-methylpyrimidines via the corresponding 2-aldoximes was not general for the reasons discussed in Section III-d. Namely, 4-cyano-2-methylpyrimidines (98) were selectively obtained from 6-substituted 2,4-dimethylpyrimidines (14), via 4-aldoximes (74), in this way. The nucleophilic reactions of pyrimidine N-oxides are not always convenient as preparative methods. Among many reactions of the N-oxides, the Reissert-Henze reaction is recommended for the synthesis of 2-cyanopyrimidines.[63,64] For example, the reaction of 4-alkoxyl-6-methylpyrimidine 1-oxides (99) with potassium cyanide in the presence of benzoyl chloride afforded 4-alkoxy-6-methylpyrimidine-2-carbonitriles (100) in excellent yields. The Reissert-Henze reaction of pyrimidine N-oxides tends to give 2-cyanopyrimidines rather than 4-cyanopyrimidines. In the case of 4-phenylpyrimidine 1-oxide (101), the ratio of the 2- (97) and 4-cyano

(102) derivatives was observed to be 2:1[6] although 4-methoxypyrimidine 1-oxide was reported to give 4-methoxypyrimidine-2-carbonitrile as the sole product.[65]



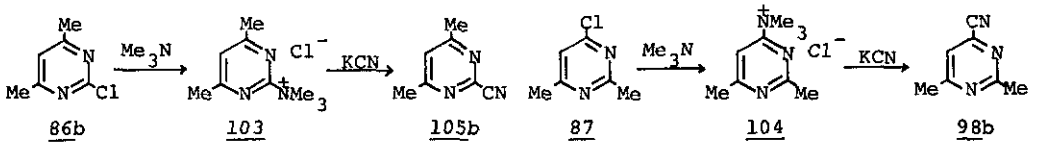
a: R_6=H 67 % bp 92-93°(15 mmHg)
b: Me 56 *bp* 113-115°(29 *mmHg*)
c: Ph 64 mp 96-98°
d: OEt 79 mp 52-52.5°
e: NMe_2 96 mp 140-141°



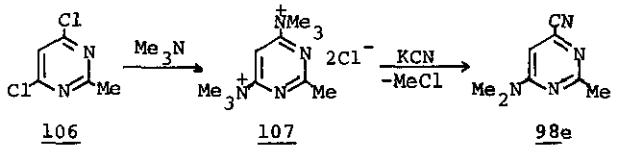
Scheme 19

Simple chloropyrimidines react slowly with trimethylamine in benzene or acetone to give quarternary salts. Triethylamine is known not to react with the chloride. For example, 2-chloro-4,6-dimethyl- (86b) and 4-chloro-2,6-dimethyl-pyrimidine (87) gave 4,6-dimethyl-2-pyrimidinyl- (103) and 2,6-dimethyl-4-pyrimidinyl-trimethyl-ammonium chloride (104) respectively.[68] When the reaction was attempted at 100°, methyl chloride was lost and the product was the dimethylamino derivative.[68]

The reactivity of the salts (103,104) with a variety of nucleophilic reagents seems to be excellent and the reaction with potassium cyanide led to replacement of the entire quaternary group with cyano group.[70] Thus, 4,6-dimethylpyrimidine-2-carbonitrile (105b) and 2,6-dimethylpyrimidine-4-carbonitrile (98b) are easily prepared by this method.[70,71]

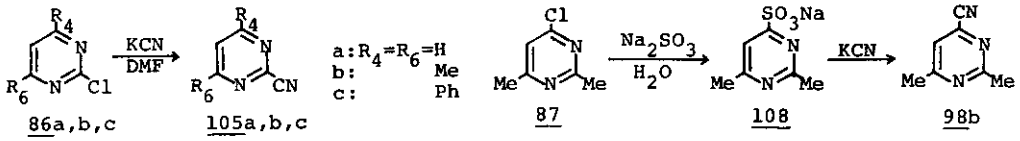


4,6-Dichloro-2-methylpyrimidine (106) reacted with excess trimethylamine to give the bis-ammonium salt (107). The reaction of 107 with potassium cyanide in the above manner did not afford the dinitrile and 6-dimethylamino-2-methylpyrimidine-4-carbonitrile (98e) was obtained with the loss of methyl chloride.[54,57]

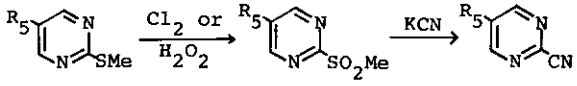


Thus, the preparation of cyanopyrimidines through quarternary salts can be regarded as a useful method because of the ready availability of starting materials and the wide applicability.[52,67-73]

Mamaev et al. have obtained 2-cyanopyrimidines (105) directly from 2-chloropyrimidines (86) by reaction with potassium cyanide.[69] However, nucleophilic substitution of sulfur containing derivatives with potassium cyanide has been rather popular for the preparation of cyanopyrimidines.[63,74-78] For example, 4-chloro-2,6-dimethylpyrimidine (87) reacted with sodium sulfite in an aqueous medium to give the sulfonate (108), which was converted into 2,6-dimethylpyrimidine-4-carbonitrile (98b),[78] and the 2-methylsulfonylpyrimidines (110), obtained by oxidation of the methylthiopyrimidines (109), were also converted into the 2-cyanopyrimidines (111) by treatment with potassium cyanide.[75-77]



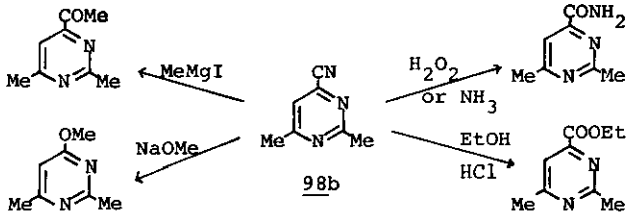
86a,b,c 105a,b,c 87 108 98b



109 110 111

Scheme 20

The chemical properties of 2- and 4-cyanopyrimidines are very similar to those of the common aromatic nitriles,[70,79] so that various side-chain derivatives were conveniently synthesized from these nitriles. The reaction of these nitriles with sodium methoxide is exceptional, and the corresponding methoxyl compounds were quantitatively obtained[79] while the same reaction of 2-(or 4-)cyanopyridines afforded ethyl 2-pyridinecarboximidate.[80] The reactions of 2,6-dimethylpyrimidine-4-carbonitrile (98b), as typical example, are illustrated in Scheme 21.



98b

Scheme 21

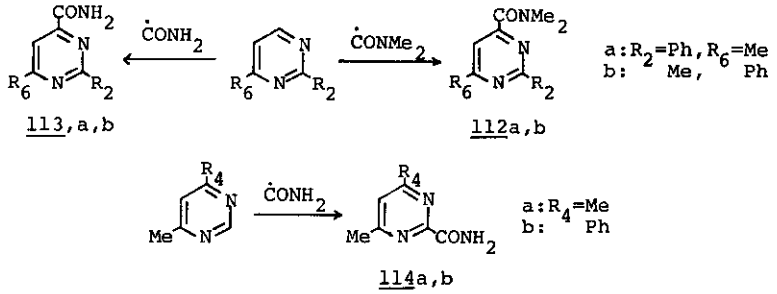
V-b Synthesis of Pyrimidine Carboxamides and Esters by Homolytic Reaction

On account of the presence of a hydrogen atom in the formyl group, formamide, N-alkyl- and N,N-dialkyl-formamide, like aldehyde in the acyl radical generation can be utilized as a source of amide radicals. In addition to this, the ethoxycarbonyl radical is produced by the reaction of ethyl pyruvate with hydrogen peroxide and ferrous sulfate in dilute sulfuric acid. These two methods reported by Minisci and co-workers are represented by the following equations (Methods D and E).[20-23]

Method D: $RR'NCHO + t\text{-}BuOOH + FeSO_4$ (for amidation)

Method E: $MeCOCOOEt + H_2O_2 + FeSO_4$ (for ethoxycarbonylation)

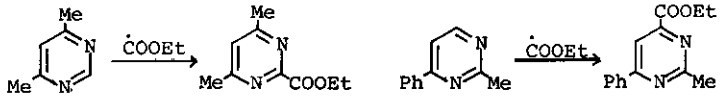
Pyrimidines with an amide group or an ester group at the 2- or 4-position can be synthesized by these methods.[59] For example, 2-methyl-6-phenylpyrimidine was converted into 2-methyl-6-phenylpyrimidine-4-carboxamide (113b) in 93 % yield under the conditions of Method D. Similarly, 6-methyl-2-phenylpyrimidine gave the corresponding amide (113a) in 75 % yield. Although the N,N-dimethylamides (112a,b) were obtained from the same pyrimidines by reaction with N,N-dimethylformamide (DMF), the yields did not exceed 40 %.



Scheme 22

Unlike the acylation of 4,6-disubstituted pyrimidines with acetyl radical, the direct amidation of the same pyrimidines did not give any 2,5-diamides, but afforded 4,6-disubstituted pyrimidine-2-carboxamides (114a,b) as the sole products.

The ethoxycarbonylation of simple pyrimidines, in general, gave unsatisfactory results.[59] The ethoxycarbonylation of 4,6-dimethyl- and 2-methyl-6-phenyl-pyrimidines, illustrated in Scheme 23, are the best examples from several trials.



Scheme 23

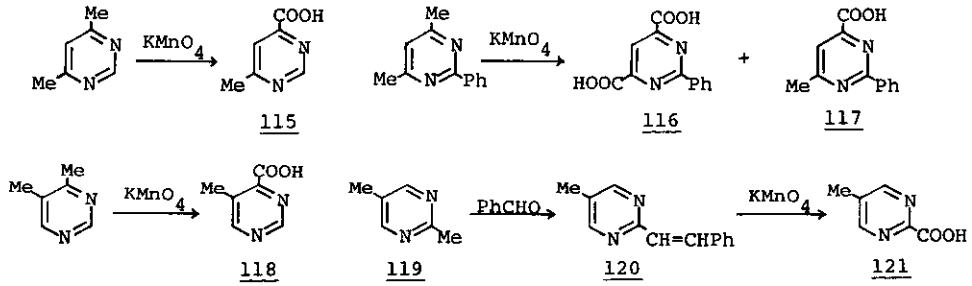
Thus an alternative procedure with experimental simplicity, instead of the homolytic ethoxycarbonylation, is necessary.

Based on the results described in this section, it is concluded that only the introduction of a primary amide group into the 4-position is practical among these three homolytic reactions.

V-c Synthesis of Pyrimidinecarboxylic Acids by Oxidation of Methyl Group

Although there are a number of papers dealing with the permanganate oxidation of methylpyrimidines,[10,42,67,81,82] the selectivity of the reaction was not clear up to the present. For example, 4,6-dimethylpyrimidine was reported to give 6-methylpyrimidine-4-carboxylic acid (115) on oxidation with a limited amount of potassium permanganate,[81] while the oxidation of 4,6-dimethyl-2-phenylpyrimidine is known to give 2-phenylpyrimidine-4,6-dicarboxylic acid (116) together with 6-methyl-2-phenylpyrimidine-4-carboxylic acid (117).[42]

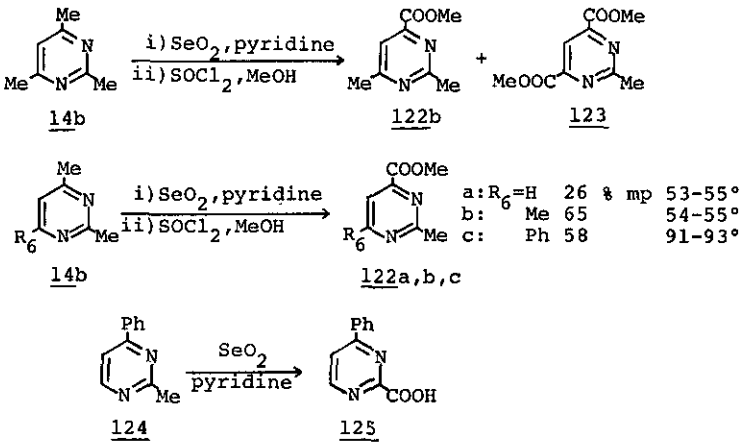
The permanganate oxidation of 4,5-dimethylpyrimidine afforded 5-methylpyrimidine-4-carboxylic acid (118),[82] which suggested the possibility of site-selective oxidation. On the other hand, 5-methylpyrimidine-2-carboxylic acid (121) was prepared by the oxidation of 5-methyl-2-styrylpyrimidine (120) after converting 2,5-dimethylpyrimidine into 120.[83] Accordingly, permanganate oxidation can not be recommended for the preparation of pyrimidine-monocarboxylic acids from polymethylpyrimidines.



Scheme 24

4-Methylpyrimidines are generally oxidized to pyrimidine-4-carboxylic acids when they are treated with selenium dioxide in warm pyridine.[84,85] The oxidation of 2,4,6-trimethylpyrimidine (14b) and subsequent esterification with the aid of thionyl chloride in methanol gave mainly 2,6-dimethylpyrimidine-4-carboxylate (122b), together with a small amount of dimethyl 2-methylpyrimidine-4,6-dicarboxylate (123). The above result suggested the existence of site-selectivity in this reaction. The oxidation of other 2,4-dimethylpyrimidines in this manner, gave results supporting the above suggestion, as shown in Scheme 25.

2-Methylpyrimidines were also oxidized when no 4-methyl group was present in the molecule (124 ⟶ 125).[86]



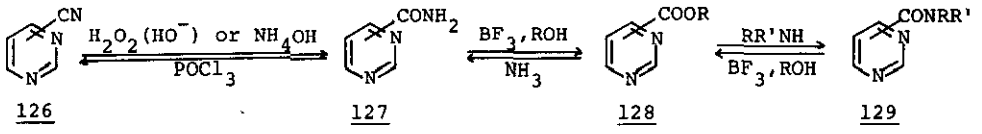
Scheme 25

V-d Interconversion of Introduced Groups

As described above, effective methods for the preparation of cyanopyrimidines have been found. Homolytic amidation with formamide is regarded as one method for pyrimidine-4-carboxamide preparation. The oxidation of 4-methylpyrimidines with selenium dioxide gave the pyrimidine-4-carboxylic acids usually in good yield.

On the other hand, homolytic amidation with DMF, rather than formamide, does not always give the tertiary amide in satisfactory yield. Moreover, homolytic ethoxycarbonylation with ethyl pyruvate generally gave poor results. The synthesis of pyrimidine-2-carboxylic acids can not be expected from the oxidation of 2,4-dimethylpyrimidines.

From this point of view, the interconversion of these groups, on the active positions of a pyrimidine ring, is necessary in order to have freedom for the preparation of pyrimidinecarboxylic acids and related compounds. Cyanopyrimidines, readily obtained by various methods, are already known to be convertible to the primary amides on the action of aqueous ammonia[70] or hydrogen peroxide in alkaline media.[79] The conversion of the same nitriles into the ethyl esters, via the corresponding ethyl imidates, was also reported.[79] In addition to these reactions,



Scheme 26

mutual transformation of these functional groups was successfully achieved as shown in Scheme 26.

VI SELECTIVITY OF REACTIONS ON PYRIMIDINE RING

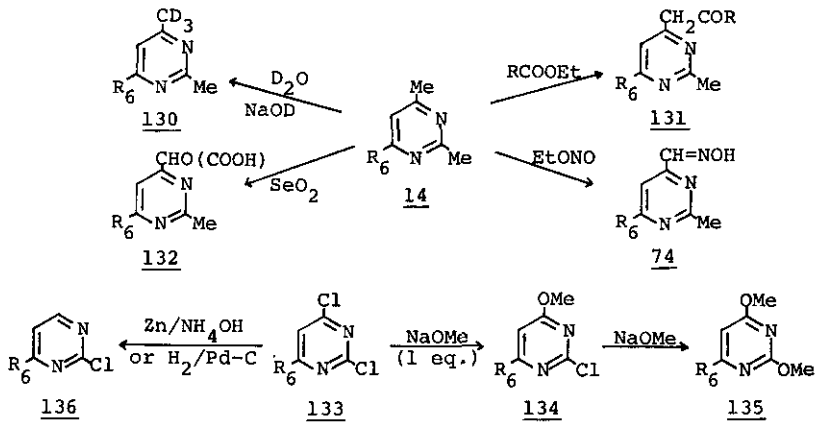
Since the π-electron density is affected by the electron-withdrawing nature of the ring nitrogen atom, there is a sharp line between the reactivity of position 3 and that of position 2 or 4 of a quinoline ring. However, the difference between the reactivity of the 2-position and the 4-position in substitution reactions is not clear. The present authors frequently observed remarkable site-selectivity of the various reactions carried out on pyrimidine derivatives. This Chapter deals with reactions considered to be examples in this category.

When a CD_3OD-D_2O solution of a 2,6-dimethylpyrimidine derivatives (14) was heated at an appropriate temperature for an appropriate period in an NMR tube, the relative acidity of the two methyl groups in a single molecule was determined by measuring the time-dependent decrease of the intensity of the signals due to the methyl hydrogen concerned. According to this method, the acidity of the 4-methyl group was always observed to exceed that of the 2-methyl group in many 6-substituted 2,4-dimethylpyrimidines (14⟶130). Thus, reactions proceeding via pyrimidinemethylene anion intermediate are expected to give mainly the 4-substituted products.[56,94]

The nitrosation of 14 to 74, described in Section III-d, is a reflection on the nature of these methyl groups.[56] Similar results were obtained from the ester condensation of 14 under basic conditions to give the 4-acylmethyl derivatives (131), predominantly.[94]

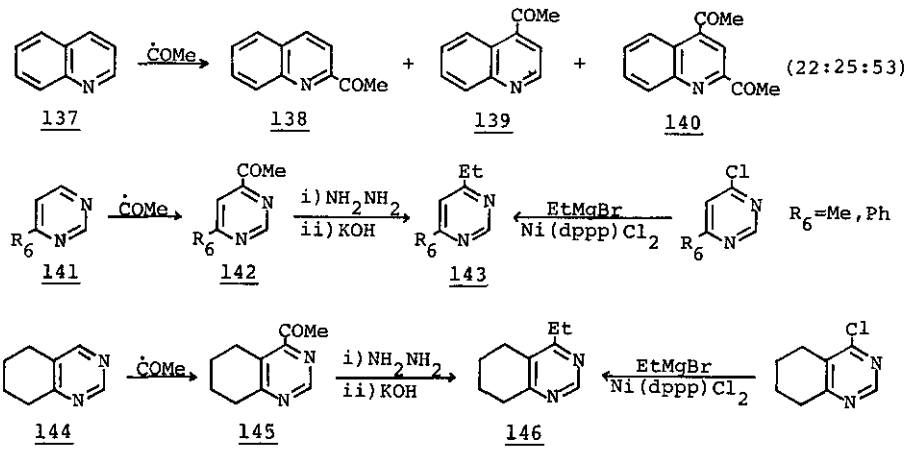
Since the mechanism of the oxidation of methylpyrimidines with selenium dioxide is not known in detail, no theoretical comment can be made on the relation between the acidity of the methyl groups and the structure of the products. However, the reagent showed a definite affinity for the 4-methyl group, to give 132 for example.

As examples of reactions occurring directly at the nuclei, it is well known that the reaction of 2,6-dichloropyrimidines with various nucleophiles affords firstly the 4-substituted products. Namely, 2,4-dichloropyrimidines (133) reacted with a limited amount of sodium methoxide to give 2-chloro-4-methoxypyrimidines (134),[65,87,88] while the reaction with excess reagent gave rise to 2,4-dimethoxypyrimidines (135). Reduction with zinc in aqueous ammonia or hydrogenation on palladium charcoal converted 133 into 2-chloropyrimidines (136) as illustrated in Scheme 27.[6,89-91]



Scheme 27

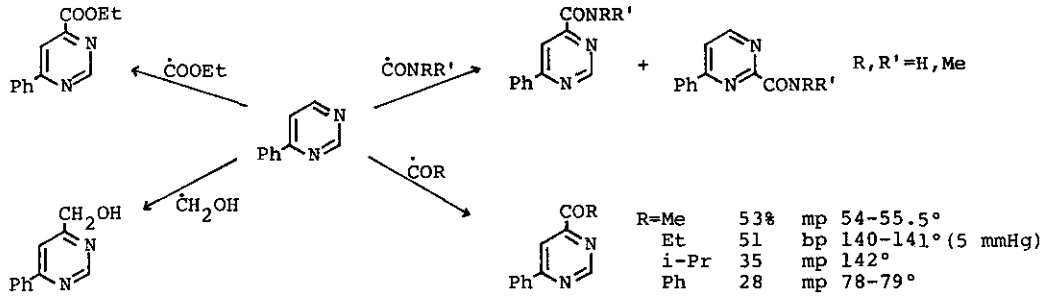
Even in case of homolytic reaction, the same selectivity is observed. Minisci and co-workers reported the reaction of quinoline (137) with the acetyl radical, generated by Method C, to give 2-acetyl- (138), 4-acetyl- (139), and 2,4-diacetyl-quinoline (140) in a ratio of 22:25:53.[19] This suggested that there is no site-selectivity in a quinoline ring. On the contrary, the pyrimidine derivatives (141), in which the 2- and 4-positions are both free reacted with the same radical to give the corresponding 4-acetyl derivatives (142).[86,92] This surprising contrast was confirmed by the reaction of 5,6,7,8-tetrahydroquinazoline (144) with the acetyl radical. The steric hindrance due to the hydrogen atom at the peri-position did not prevent the introduction of acyl group to the 4-position. The structures of these products (142,145) were established by their reduction to the corresponding



Scheme 28

4-ethyl derivatives (143,146).

On the basis of the above experiments, further attempts were made as shown in Scheme 29.[86,92] Namely, 6-phenylpyrimidine was allowed to react with various radicals and products were always the 4-substituted 6-phenylpyrimidines. In the case of reaction with the N,N-dimethylaminocarbonyl radical, the pyrimidine-2-carboxamide was obtained as a minor product.



Scheme 29

Since the one-step preparation of 6-phenyl(or 6-alkyl)pyrimidines has already been established by Bredereck et al.,[93] the selective synthesis of 4-acyl-6-phenylpyrimidines from 6-phenylpyrimidine in this way seems to be practical. The experimental data are summerized in Scheme 29.

Based on the results described in this section, it is recognized that there is a greater difference between the 2- and 4-positions of the pyrimidine ring than there is between the same positions of the quinoline ring. The difference in the case of pyrimidines is large enough to control the direction of substitution. Readers who carefully survey the literature will be able to find a lot of other examples which indirectly show the site-selectivity of pyrimidine compounds. The authors think this site-selectivity will be utilized much more in the synthesis of pyrimidine derivatives.

Until a few years ago, the synthesis of simple pyrimidine derivatives with carbon functions such as CH_2OH, CHO, COR, COOR, $CONR_2$, and CN at the 2- or 4-position was quite problematic. However, from the work described in this paper, it can now not be said that this is still the case in this field. The authors wish and expect rapid progress to be made in this field in the near future.

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