SYNTHESIS AND REACTIONS OF N-SUBSTITUTED 2(1H)-PYRIMIDINONES AND PYRIMIDINETHIONES

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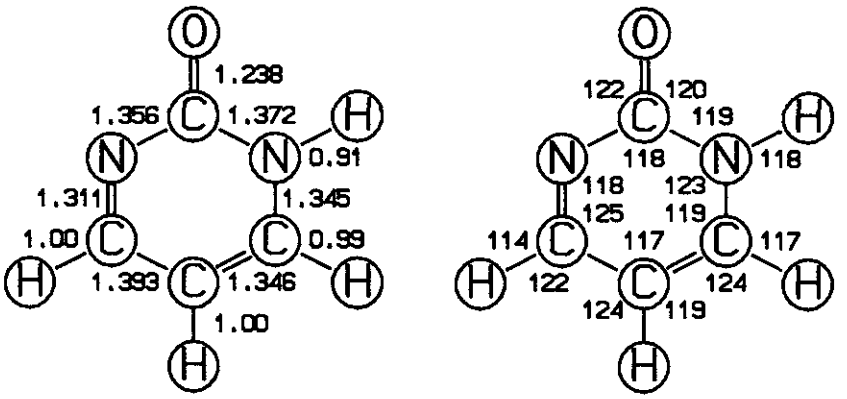
Abstract —— The synthesis of N-substituted 2(1H)-pyrimidinones and pyrimidinethiones bearing various substituents is discussed. The regioselective substitution of C-6 methyl protons of N-substituted 4,6-dimethyl-2(1H)-pyrimidinones is observed by the treatment with electrophiles such as alkyl halides and benzenediazonium salt. The ring transformations to benzene, isoxazole, pyrazole, triazole, pyridine, and pyrimidine by the reaction of title compounds with a variety of nucleophiles are reviewed. Dihydro- and tetrahydro-2(1H)-pyrimidinones and the corresponding thiones are regioselectively obtained by reaction with organometallic reagents and metal hydride complexes. The photochemical behaviors of N-substituted 2(1H)-pyrimidinones are also reviewed.

2(1H)-Pyrimidinone is an unsaturated six-membered ring containing four ring carbons including a carbonyl carbon and two ring nitrogens. The structure has already been confirmed to be a nearly planar heterocyclic compound by means of X-ray crystallographic method.[1,2]

The tautomerism between diazinones and hydroxy-diazines has extensively been investigated in connection with nucleic bases such as uracil and cytosine. 2(1H)-Pyrimidinone is tautomeric with 2-hydroxypyrimidine. The tautomerism of 2(1H)-pyrimidinone has been investigated by comparison of the spectral data of 1-methyl-2(1H)-pyrimidinone and 2-methoxypyrimidine, which are the fixed model compounds of each tautomeric form. By the UV and IR spectroscopic technique, the predominant tautomer was concluded to be the lactam form in 2(1H)-pyrimidinone.[3-6] Recently this fact was also supported by the following ^{1}H- and ^{13}C-NMR spectral data.[7,8] The chemical shift of methine proton of (1) in ^{1}H-NMR

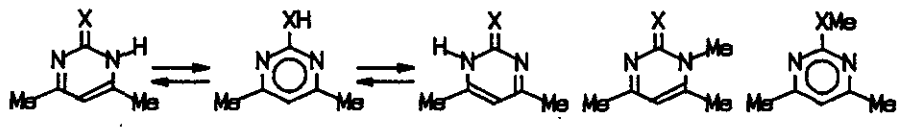


Bond Length (Å) Bond Angle (deg)

Figure 1

was essentially the same with that of the corresponding 1-methyl derivative (2). When ^{13}C-NMR spectrum of (1) was compared with those of (2) and (3), the C-2 carbon signal of (1) also appeared close to that of (2) rather than that of (3). The similar tendency was observed in the C-5 carbon signals. By the spectroscopic comparison with model compounds (5) and (6), 2(1H)-pyrimidinethione (4) was also found to exist in the lactam form predominantly.

Table 1



a b c

X= O	(1)		(2)	(3)
X= S	(4)		(5)	(6)

Comp.	^{1}H- and ^{13}C-NMR Chemical Shift (ppm)							Lactam
	H-5	C-2	C-4	C-6	C-5	Me-4	Me-6	%
(1)	6.20	160.2	165.5		105.3	22.0		76
(2)	6.18	157.5	174.0	157.1	105.8	24.9	20.5	
(3)	6.68	169.0	165.4		113.7	23.8		

Further, the slow prototropic interconversion between N-1 and N-3 nitrogens via the lactim form (b in Table 1) was observed.[7]

Biologically important pyrimidine bases such as cytosine, uracil, and thymine, also exist in the lactam form. Moreover, N-substituted 2(1H)-pyrimidinones are regarded as analogous compounds for nucleosides, because they have the substituents such as D-ribosyl or 2-deoxy-D-ribosyl group on N-1 position. Under these situations, it is quite necessary to introduce the substituents at N-1 position for the purpose of the studies on the lactam form of 2(1H)-pyrimidinones.

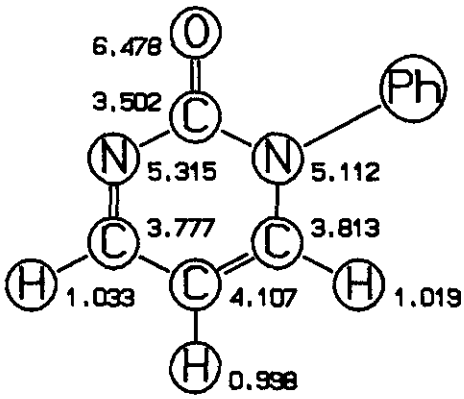


Figure 2

Generally the electron density is the good index for studying the chemical behavior of organic molecules. The resulting atomic population of 1-phenyl-2(1H)-pyrimidinone by INDO calculation is shown in Figure 2.[9] The carbonyl oxygen, N-1 and N-3 nitrogens, and C-5 olefinic carbon are expected to be attacked by electrophiles, while C-2, C-4, and C-6 carbons are prone to be attacked by nucleophiles. From the differences of the electron densities on C-2, C-4 and C-6 carbons, 2(1H)-pyrimidinones are expected to react regioselectively with nucleophiles like as α,β-unsaturated imines, which are considered to be the partial structure of 2(1H)-pyrimidinones.

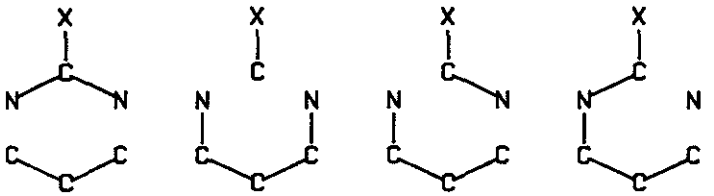
The chemistry of pyridine, pyridone, and pyrimidine has already been reviewed.[10-13] However, the review concerning to 2(1H)-pyrimidinones and 2(1H)-pyrimidinethiones especially N-substituted derivatives has never been reported.

In this paper, we wish to review the syntheses and reactions of N-substituted 2(1H)-pyrimidinones and pyrimidinethiones including the electrophilic, nucleophilic and photochemical reactions.

I Synthesis of N-Substituted 2(1H)-Pyrimidinones and Pyrimidinethiones

Although many papers have been reported on the synthesis of N-substituted 2(1H)-

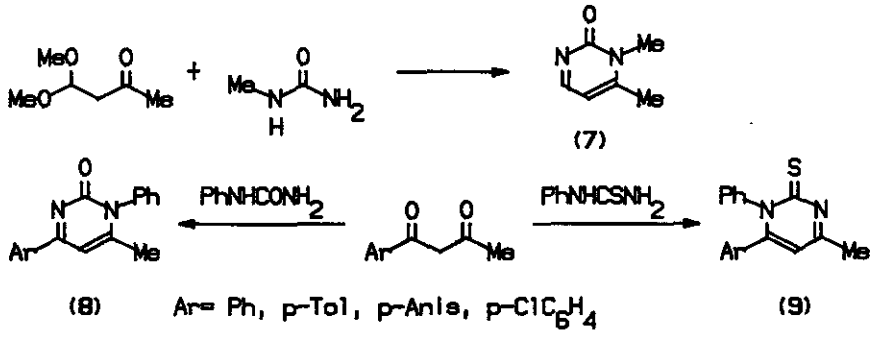
pyrimidinones and pyrimidinethiones, few papers concerning the selective synthesis of "unsymmetrical" N-substituted 2(1H)-pyrimidinones which have different substituents at C-4 and C-6 position of the ring, have been reported. The synthetic methods for the construction of the pyrimidinone ring are classified into four categories illustrated in Figure 3. Here, the regio-selective syntheses of the unsymmetrical 2(1H)-pyrimidinones and pyrimidinethiones are predominantly reviewed.



X= O, S

Figure 3

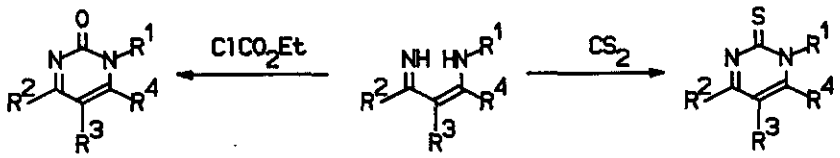
According to Type 'A', various N-substituted 2(1H)-pyrimidinones and pyrimidinethiones have been synthesized by the reaction of β-diketones[14-31], β-aminoenones[32,33], and ynones[34,35] with ureas and thioureas. Especially the condensation of β-diketones with ureas under acidic conditions is the oldest



Scheme 1

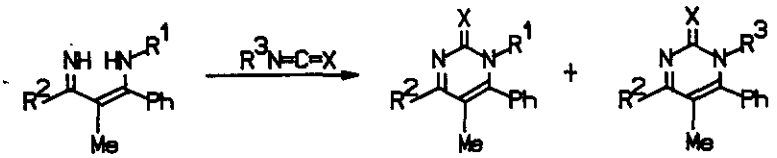
and the most general method for N-substituted 2(1H)-pyrimidinones. However, this method is seemed to be unsuitable for the selective synthesis of unsymmetrical 2(1H)-pyrimidinones because of the similar chemical property between two carbonyl groups of β-diketones and/or between two nitrogens of ureas. A few synthetic examples for unsymmetrical 2(1H)-pyrimidinones have been presented in the literature. Acetoacetaldehyde dimethylacetal reacted with N-methylurea to give 1,6-dimethyl-2(1H)-pyrimidinone (7).[30] N-Phenylurea was subjected to treatment with benzoylacetone derivatives to give mainly 1,4-diaryl-6-methyl-2(1H)-pyrimidinones (8), while N-phenylthiourea afforded only 1,6-diaryl-4-methyl-2(1H)-pyrimidinethiones (9) in good yields.[31] Also the condensation of benzoylacetylene with N-benzylthiourea gave unsymmetrical 1-benzyl-4-phenyl-2(1H)-pyrimidinethione (10) in 95% yield. (Scheme 1)

Type 'B' synthesis have been developed by J. Barluenga and co-workers using di-imines as the N-C-C-C-N component.[36-38] Di-imines were treated with ethyl chloroformate in pyridine at room temperature to give 2(1H)-pyrimidinones (11). Di-imines were heated with carbon disulfide to afford 2(1H)-pyrimidinethiones



(11) (12)

R^1= Ph, Hex, p-Tol, o-Tol
R^2= Ph, p-ClC_6H_4, p-Tol, Hex
R^3= H, Me
R^4= Ph, p-ClC_6H_4



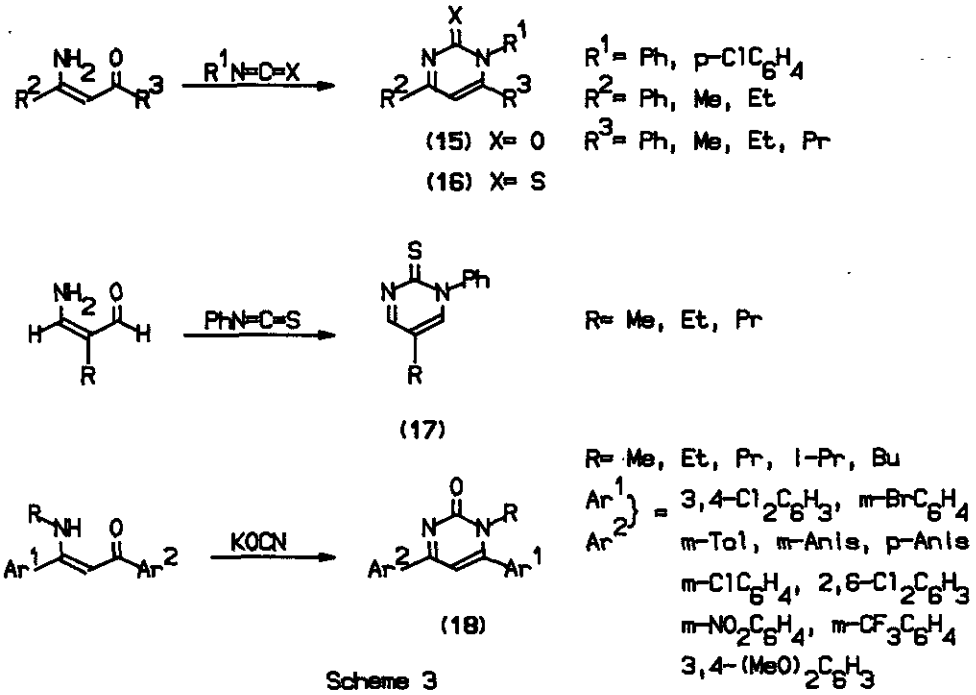
X= O, S (13) (14)

R^1= Ph, o-Tol, p-Tol, Hex
R^2= Ph, p-Tol
R^3= Ph, Bu, Hex

Scheme 2

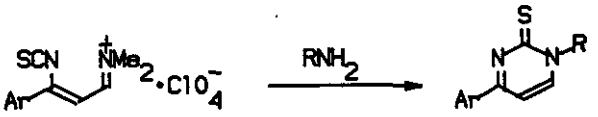
(12) in high yields.[36] (Scheme 2) The treatment of di-imines with isocyanate or isothiocyanate gave a mixture of two products (13) and (14). The ratio of (13) and (14) depends upon the substituents R^1 and R^3.[37]

Type 'C' synthesis involves the reaction of β-amino-α,β-unsaturated ketones or aldehydes with heterocummulenes. β-Amino-α,β-unsaturated ketones reacted with phenylisocyanate and phenylisothiocyanate to give the regioisomer of 1-phenyl-4,6-disubstituted 2(1H)-pyrimidinones (15) and pyrimidinethiones (16), respectively.[39] When α-alkyl-β-amino-α,β-unsaturated aldehydes were refluxed with phenylisothiocyanate, 1-phenyl-5-alkyl-2(1H)-pyrimidinethiones (17) were obtained.[40] The cyclization of N-alkyl substituted 1,3-diaryl-3-amino-2-propen-1-ones with potassium cyanate yielded 1-alkyl-4,6-diaryl-2(1H)-pyrimidinones (18).[41] (Scheme 3)



Scheme 3

Type 'D' synthetic procedure has been extensively investigated by J. Liebscher and H. Hartmann.[42-45] When 3-aryl-3-isothiocyanato-2-propeniminium perchlorates were allowed to react with various amines, 4-aryl-2(1H)-pyrimidinethiones (19) bearing aryl, heteroaryl, and amino groups at N-1 position were obtained in good yields. (Scheme 4) This method is excellent for the synthesis of unsymmetrical 1,4-disubstituted 2(1H)-pyrimidinethiones.



Ar= p-XC_6H_4 (X= H, Me, MeO, Cl)
2-Naphthyl

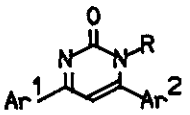
R= XC_6H_4 (X= H, 2-MeO, 3-MeO, 4-MeO, 4-Me)
2-Naphthyl, Heteroaryl

XNH X= { H, Ph, p-$NO_2C_6H_4$, p-Ts
Ac, PhCO, EtCO, EtOCO }

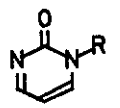
(19)

Scheme 4

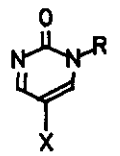
Although the most general methods for the synthesis of N-substituted 2(1H)-pyrimidinones and pyrimidinethiones fall into above four categories, there are some other synthetic methods to be worthy of comment. The alkylation of 4,6-disubstituted 2(1H)-pyrimidinones with alkyl p-toluenesulfonates,[46] diphenylmethanol,[47] nitroethylene,[48] p-substituted benzyl bromides,[49,50] and α-haloacetic acids[51,52] afforded 1,4,6-trisubstituted 2(1H)-pyrimidinones (20), (21), (22), (23), and (24), respectively. Also 5-halo-2(1H)-pyrimidinones were treated with 2-deoxy-α-D-ribofuranosyl chloride,[53] p-chlorobenzyl halomethyl ether,[54] p-chlorophenyl halomethyl thioether, [55] and propargyl halide[56] to give 1,5-disubstituted



(20) R= Me, Et, Pr, Bu



(21) R= Ph_2CH
(22) R= $CH_2CH_2NO_2$
(23) R= p-$ClC_6H_4CH_2$, p-$NH_2C_6H_4CH_2$, p-$AnisCH_2$
(24) R= CH_2CO_2H, CH_2CO_2Et

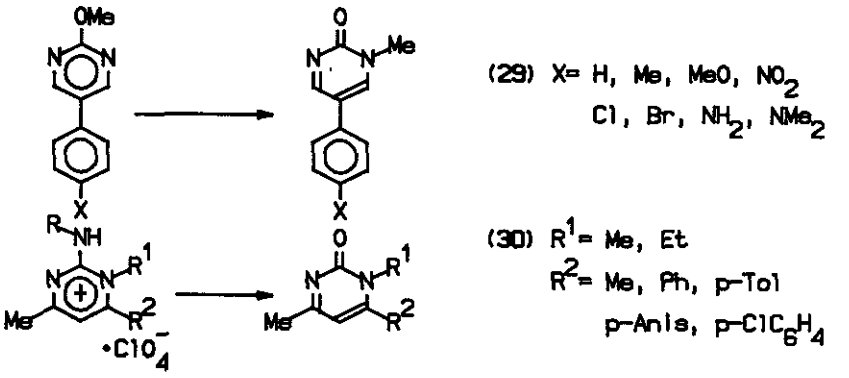


(25) R= 2-Deoxy-α-D-ribofuranosyl
(26) R= p-$ClC_6H_4SCH_2$
(27) R= p-$ClC_6H_4OCH_2$
(28) R= $HC{\equiv}CCH_2$

X= Cl, Br, I, CF_3

Scheme 5

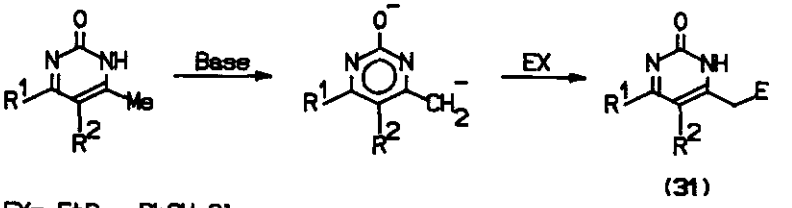
2(1H)-pyrimidinones (25), (26), (27), and (28), respectively. (Scheme 5) These methods are unsuitable for the alkylation of N-unsubstituted 2(1H)-pyrimidinethione due to the predominant formation of the alkylthiopyrimidines. The oxidation of dihydro-2(1H)-pyrimidinones with potassium permanganate,[57,58] manganese dioxide,[16,59,60] dichlorodicyano-1,4-benzoquinone (DDQ),[61,62] and tetrachloro-1,4-benzoquinone (chloranil)[63] gave the corresponding 2(1H)-pyrimidinones. The thermal rearrangement of 2-methoxypyrimidines[28,32] and the hydrolysis of 2-(N-substituted)amino-pyrimidinium perchlorate[64] also afforded N-substituted 2(1H)-pyrimidinones (29) and (30), respectively. (Scheme 6)



Scheme 6

II Reaction with Electrophiles

It is well known that methyl protons are activated by the adjacent aromatic ring, especially nitrogen containing heteroaromatic ring. The alkylation of N-



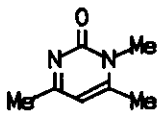
EX= EtBr, $PhCH_2Cl$
Hex-CHO, p-Anis-CHO, 3,4,5-$(MeO)_3C_6H_2CHO$, Piperonal
PhCOMe, Ph_2CO, c-Hexanone
AcOEt, $PhCO_2Me$

Scheme 7

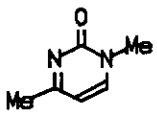
unsubstituted 6-methyl-2(1H)-pyrimidinones has been carried out by the deprotonation with butyllithium or sodium amide in liquid ammonia, and subsequent treatment of the resulting dianion with various electrophiles to give the C-alkylated 2(1H)-pyrimidinones (31).[65,66] (Scheme 7)

The rate constants for the H-D exchange of the C-methyl groups in three types of 1-methyl-2(1H)-pyrimidinones (2), (32), and (7) in alkaline deuterium oxide solution were measured by means of ^{1}H-NMR spectroscopy.[18,67,68] As the result, the H-D exchange rate of C-6 methyl protons is 20-fold or much faster than that of C-4 methyl protons. (Table 2)

Table 2



(2)



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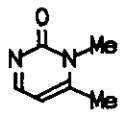


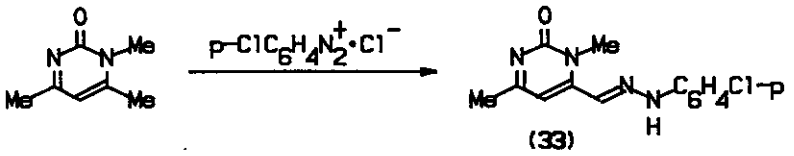
(7)

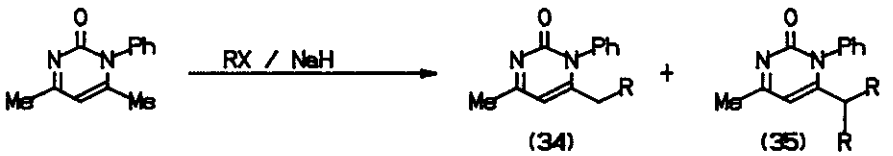
Comp.	k(M^{-1} min^{-1})		$k_{6\text{-Me}}/k_{4\text{-Me}}$
	4-Me	6-Me	
(2)	0.076	1.86	24
(32)	0.22	-	
(7)	-	4.45	20

In spite of this fact, few papers concerning the regioselective reaction on C-4 and C-6 methyl group have been reported. 1,4,6-Trimethyl-2(1H)-pyrimidinone was treated with p-chlorobenzenediazonium chloride to give the diazo coupling product (33) in 98% yield.[69] When 4,6-dimethyl-1-phenyl-2(1H)-pyrimidinone was allowed to react with alkyl halides in the presence of sodium hydride at low temperature, two kinds of the C-6 alkylated products (34) and (35) were obtained.[70] The ratio of (34) and (35) was easily controlled by changing the amount of alkyl halides. Further, 4,6-dimethyl-2(1H)-pyrimidinones having carbonyl group at N-1 position underwent the intramolecular cyclocondensation to give pyrrolopyrimidinones (36) in 73-93% yields.[71] (Scheme 8)

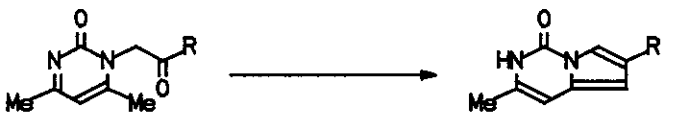
The bromination of 1-methyl-2(1H)-pyrimidinone in acidic medium occurred at C-5 position to give 5-bromo-1-methyl-2(1H)-pyrimidinone (38).[72,73] From the detailed study on the mechanism, it was found that the rate-determining step involved attack by molecular bromine upon the covalent hydrate (37), which was

proposed by A. R. Katritzky and co-workers[74] on the deuteration of C-5 carbon of 2(1H)-pyrimidinone. (Scheme 9)



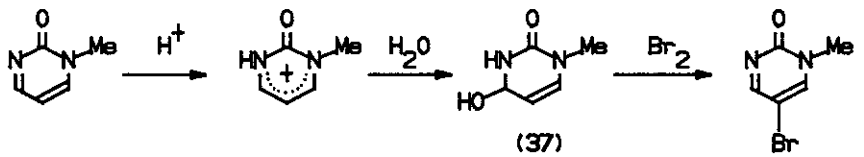


RX= MeI, EtI, $PhCH_2Br$, m-Tol-CH_2Br, p-Tol-CH_2Br, p-$BrC_6H_4CH_2Br$



R= Me, Ph, p-$NO_2C_6H_4$

Scheme 8



Scheme 9

III Reaction with Nucleophiles

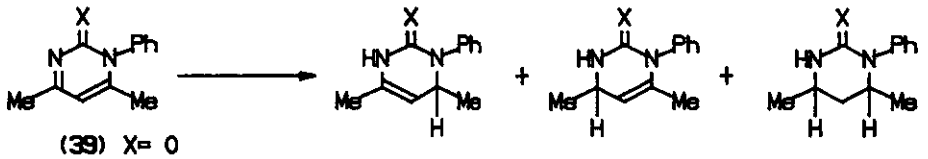
As mentioned in Introduction, it is predicted from INDO calculation that C-2, C-4, and C-6 carbons are easily attacked by nucleophiles. Since 2(1H)-pyrimidinone possesses the partial structure of α,β-unsaturated imine moiety, the regioselective reactions are also expected.

III-a Reaction with Metal Hydride Complexes

The reaction with metal hydride complexes such as sodium borohydride and lithium aluminum hydride proceeds under mild conditions.[75] 4,6-Dimethyl-1-phenyl-2(1H)-pyrimidinone (39) and pyrimidinethione (40) were facilely reduced with

metal hydride complexes at room temperature to give mixtures of 3,6-dihydro-(a), 3,4-dihydro-(b), and tetrahydro-derivatives (c) in high yields. The ratio of three products was dramatically dependent on the reaction conditions and on the nature of the C-4 and C-6 substituents in the pyrimidine ring. (Table 3)

Table 3



(39) X= O
(40) X= S

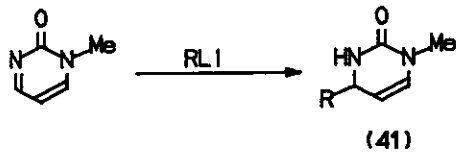
a b c

	Conditions	Yield (%)	Ratio a : b : c
X=O	$NaBH_4$-$B(OMe)_3$	90	100 : 0 : 0
	$NaBH_4$-NaOH	91	0 : 0 : 100
	$LiAlH_4$	93	30 : 70 : 0
	$LiAlH_4$/$NaBH_4$-NaOH	83	0 : 37 : 63
	$NaBH_4$-AcOH	86	0 : 0 : 100
X=S	$NaBH_4$-$B(OMe)_3$	85	100 : 0 : 0
	$NaBH_4$-NaOH	84	0 : 0 : 100
	$LiAlH_4$	90	50 : 50 : 0
	$LiAlH_4$/$NaBH_4$-NaOH	75	0 : 40 : 60
	$NaBH_4$-AcOH	85	0 : 0 : 100

These reduced 2(1H)-pyrimidinones and pyrimidinethiones are useful synthetic intermediates for the preparations of dihydropyrimidines[76,77] and chain compounds such as 1,3-diamine[78,79] or β-amino oxime.[80]

III-b Reaction with Organometallic Reagents

When organometallic reagents are used instead of metal hydride complexes, two type of dihydro-2(1H)-pyrimidinones and pyrimidinethiones are obtained. The reaction of 1-methyl-2(1H)-pyrimidinone with aryl-lithium reagents gave only 1,4-disubstituted 3,4-dihydro-2(1H)-pyrimidinones (41).[57,58] (Scheme 10)
The difference of the regioselectivity among organometallic reagents was systematically examined by the reaction with 1-phenyl-2(1H)-pyrimidinone (42).



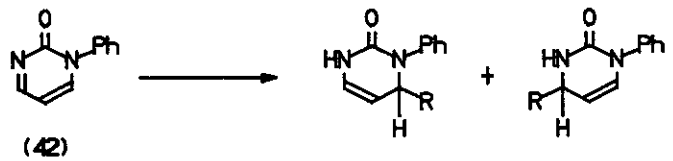
(41)

R= Ph, p-ClC$_6$H$_4$, 2-Thienyl

Scheme 10

The compound (42) was subjected to treatment with methyllithium to yield exclusively 3,4-dihydro-4-methyl-1-phenyl-2(1H)-pyrimidinone (42b), while methylmagnesium iodide gave only 3,6-dihydro-6-methyl-1-phenyl-2(1H)-pyrimidinone (42a).[81] (Table 4)

Table 4



(42) a b

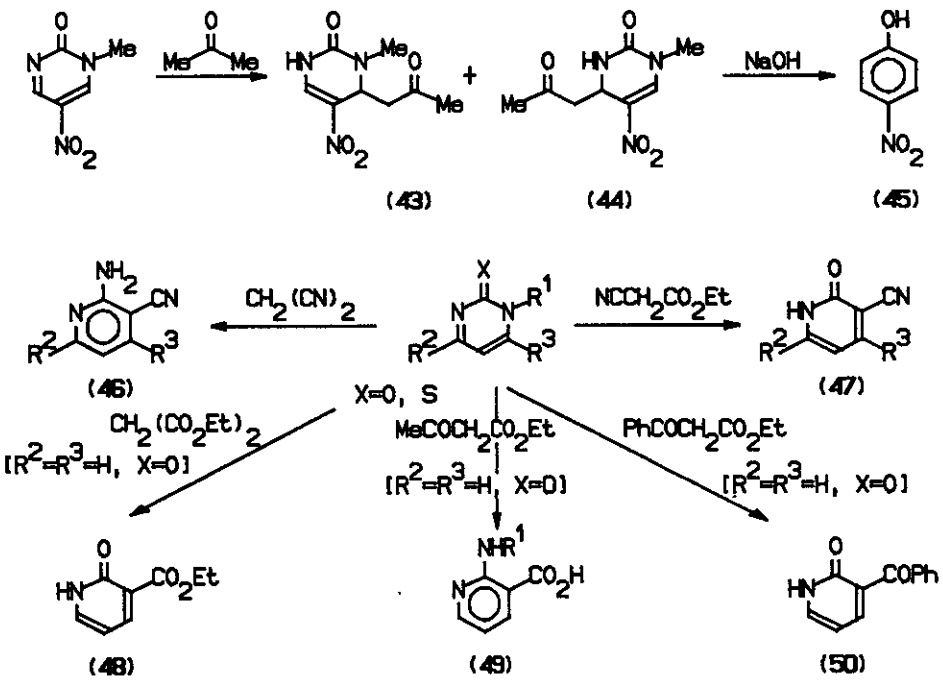
RM	Yield (%)	Ratio a	Ratio b
MeLi	88	0	100
MeMgI	59	100	0
BrZnCH$_2$CO$_2$Et	63	17	83

The bulkiness of alkyl groups of Grignard reagents has a large influence on the ratio of two types of dihydro-derivatives. 2(1H)-Pyrimidinethiones showed similar behavior to 2(1H)-pyrimidinones. Further, (42) was treated with ethyl bromoacetate in the presence of zinc (Reformatsky reaction) to afford mainly 3,4-dihydro-4-ethoxycarbonylmethyl-1-phenyl-2(1H)-pyrimidinone (42b) in addition to 3,6-dihydro-derivative (42a).[82] This result implies that the reactivity of Reformatsky reagent is very similar to that of organolithium reagent.

III-c Reaction with Active Methylene Compounds

The synthesis of a new heterocyclic ring by transformation of some other heterocyclic system is of considerable interest. The ring transformation of heterocycles except for the case of 2(1H)-pyrimidinones and their derivatives has been reviewed by H. C. van der Plas.[83] In the consideration of the results

of section III-a and III-b, it is expected that carbanion also attacks C-4 and C-6 positions in the pyrimidine ring. When 1-methyl-5-nitro-2(1H)-pyrimidinone was treated with acetone under basic condition, two kinds of dihydro-2(1H)-pyrimidinones (43) and (44) were obtained. Further (43) and (44) underwent the ring transformation to give p-nitrophenol (45) by simultaneous elimination of N-methylurea and aromatization via aci-nitro intermediate.[84] (Scheme 11) 1,4,6-Trisubstituted 2(1H)-pyrimidinones were stirred with malononitrile and ethyl cyanoacetate in the presence of sodium ethoxide to give 4,6-disubstituted 2-amino-3-pyridinecarbonitriles (46) and 2-oxo-1,2-dihydro-3-pyridinecarbonitriles (47) in high yields, respectively.[85]



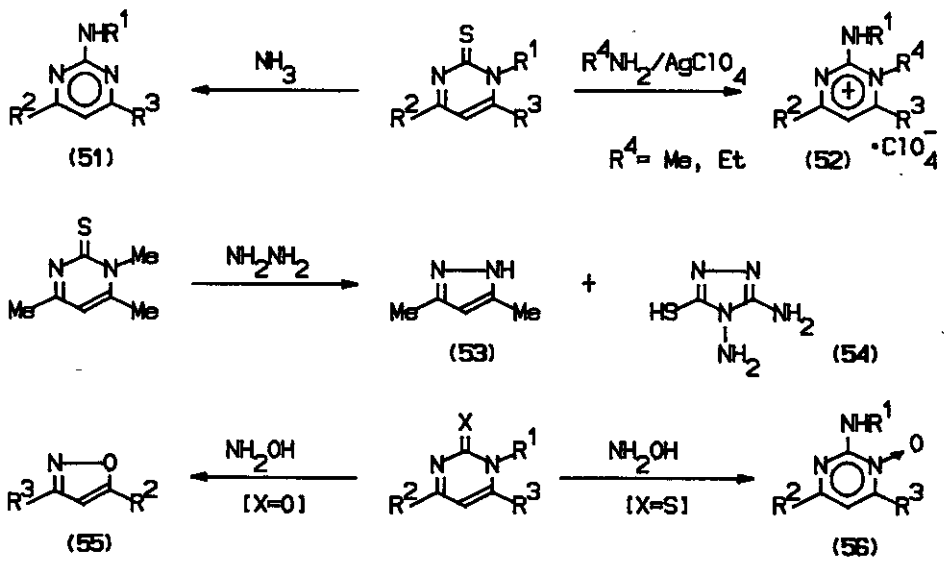
Scheme 11

The corresponding 2(1H)-pyrimidinethiones exhibited the similar chemical behaviors. In the case of 1-phenyl-2(1H)-pyrimidinone, which has no substituent at C-4 and C-6 positions of the pyrimidine ring, ring transformation proceeded to give ethyl 2-oxo-1,2-dihydro-3-pyridinecarboxylate (48). Similarly the reaction of 1-phenyl-2(1H)-pyrimidinone with ethyl acetate and ethyl

benzoylacetate afforded pyridine derivatives (49) and (50), respectively. (Scheme 11) However when 4,6-dimethyl-1-phenyl-2(1H)-pyrimidinone reacted with diethyl malonate, the starting material was recovered. These results imply that the active methylene compounds are susceptible to the steric effect. Also it is indicated that a carbanion attacked selectively at C-6 position of the pyrimidine ring at the initial step.

III-d Reaction with Amines

When 1,4,6-trisubstituted 2(1H)-pyrimidinethiones were heated with ammonia in a sealed tube, Dimroth-type ring transformation occurred to give 4,6-disubstituted 2-aminopyrimidines (51) in 29-42% yields.[64] In the case of primary alkylamines in the presence of metal perchlorate, the products (52) were isolated as perchlorate salts. (Scheme 12) The corresponding 2(1H)-pyrimidinones did not undergo ring transformation under similar conditions. 1,4,6-Trimethyl-2(1H)-pyrimidinone was treated with hydrazine to give 3,5-dimethylpyrazole (53) and N-aminotriazole (54).[86] Further the interesting ring transformation was observed

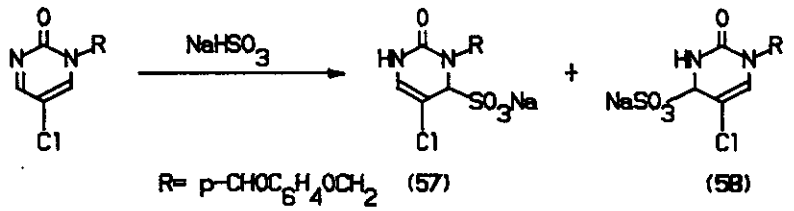


Scheme 12

on the reaction with hydroxylamine instead of hydrazine. 1,4,6-Trisubstituted 2(1H)-pyrimidinones were treated with hydroxylamine to afford 3,5-disubstituted isoxazoles (55) in 66-80% yields by the elimination of ureas. On the other hand, 2(1H)-pyrimidinethiones gave mainly 2-(N-substituted)aminopyrimidine 1-oxides (56) in considerable yields.[87] (Scheme 12)

III-e Reaction with Sodium Bisulfite

It is well recognized that sodium bisulfite readily reacts with aldehydes and some ketones to give bisulfite addition products. Similarly 5-chloro-1-(p-formylphenoxy)methyl-2(1H)-pyrimidinone was stirred at room temperature in aqueous sodium bisulfite to afford isomeric bisulfite addition products (57) and (58).[88] (Scheme 13)



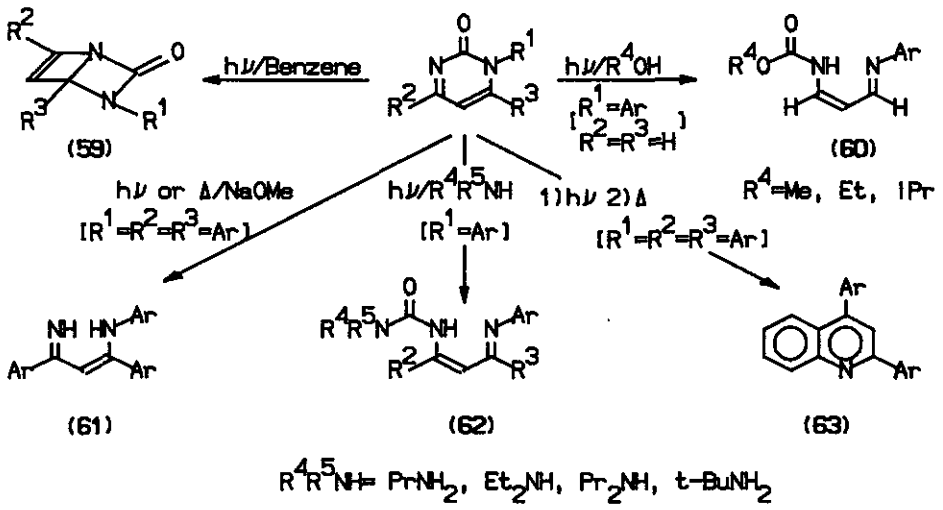
Scheme 13

IV Photochemical Reaction

The photochemistry of nucleoside bases and their derivatives is an area of significant importance for understanding the photo-reactivity of nucleic acids and this area has been extensively studied.[89-91] It is also of interest to study the photochemical reactions of 2(1H)-pyrimidinones related to cytosine and its derivatives. K.-H. Pfoertner reported the photochemical alcohol addition and dimerization of N-unsubstituted 2(1H)-pyrimidinone.[92]

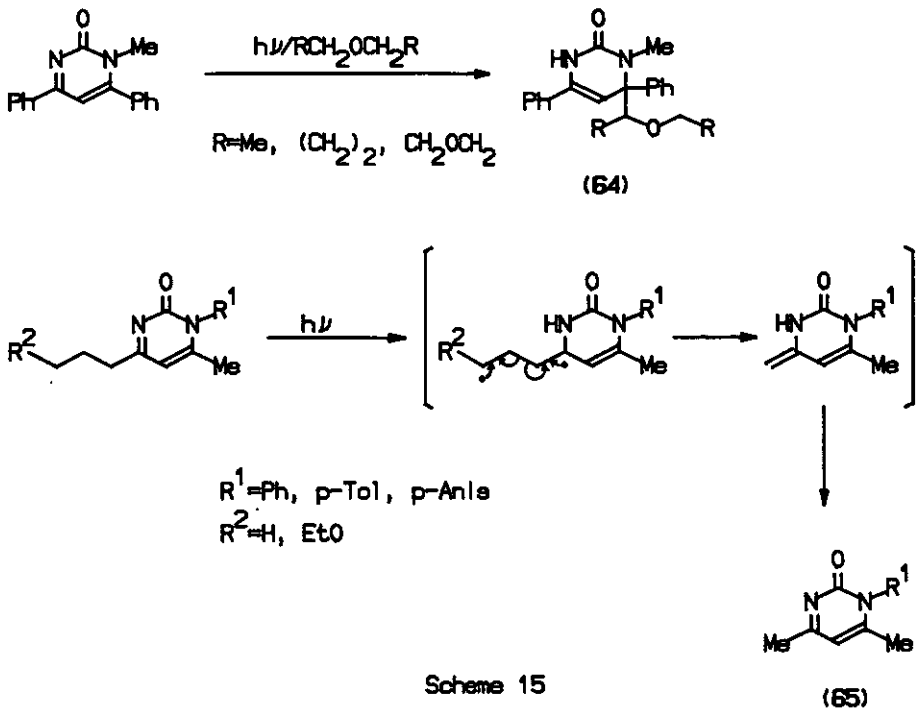
The photochemical reactions of N-substituted 2(1H)-pyrimidinones have been intensively investigated by T. Nishio and co-workers. When 1,4,6-trisubstituted 2(1H)-pyrimidinones in benzene were irradiated with a high pressure mercury lamp under an argon atmosphere, the photochemical electrocyclization products, 2-oxo-1,3-diazabicyclo[2.2.0]hex-5-enes (59) were obtained in 14-85% yields.[93,94] Irradiation of N-aryl-2(1H)-pyrimidinones, having no substituent at C-4 and C-6

position, in a mixed benzene-alcohol solution gave the photochemical ring opening products (60) in 45-55% yields.[95,96] Further, irradiation of 1,4,6-trisubstituted 2(1H)-pyrimidinones in the presence of alkoxides or primary and secondary amines also afforded the ring opening products (61) or (62).[38,97] Especially di-imines (61) are versatile starting materials for the synthesis of heterocycles. The initial step for the formation of three products (60), (61), and (62) is explained in terms of the Norrish Type I cleavage of R^1N-CO bond. By photochemical and subsequent thermal reactions of 1,4,6-triaryl-2(1H)-pyrimidinones, 2,4-diarylquinolines (63) were obtained in a one-pot in 20-53% yields.[98,99] (Scheme 14)



Scheme 14

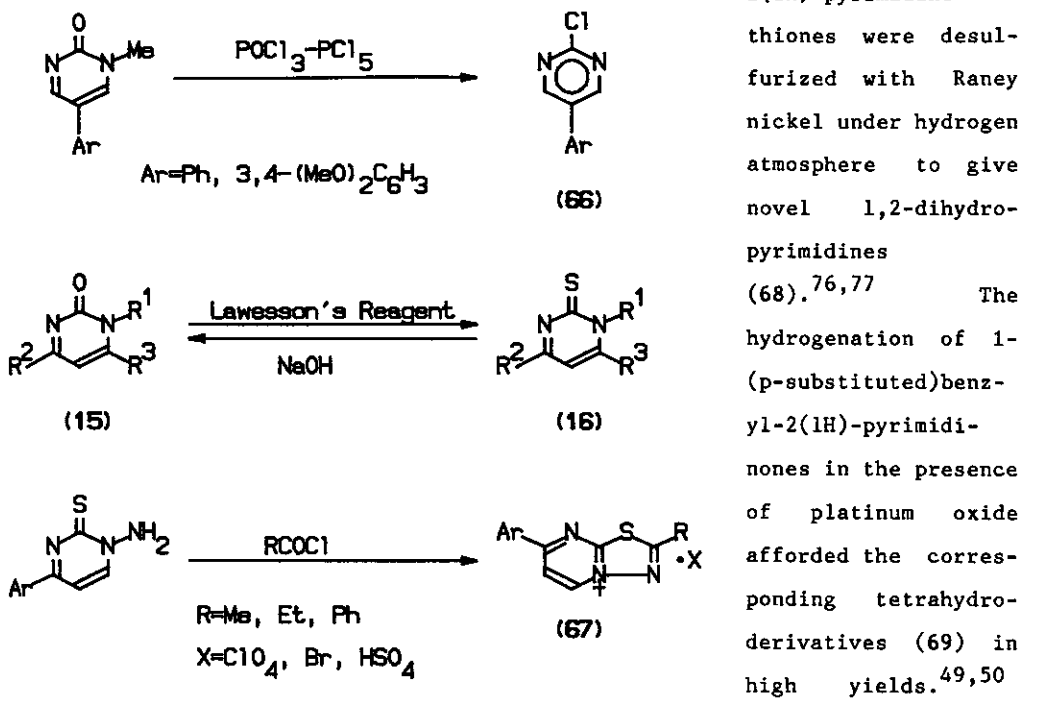
The inter- and intramolecular hydrogen abstraction by the excited imino nitrogen of 2(1H)-pyrimidinones was also reported. For example, irradiation of 1-methyl-4,6-diphenyl-2(1H)-pyrimidinone in acyclic or cyclic ethers gave the C-C bonded 1:1 adducts (64) in 45-65% yields via intermolecular hydrogen abstraction.[100] On the other hand, irradiation of 1-aryl-4-propyl- and 1-aryl-4-(3-ethoxypropyl)-6-methyl-2(1H)-pyrimidinones afforded the photoelimination products (65) via intramolecular γ-hydrogen abstraction.[101] (Scheme 15)



Scheme 15

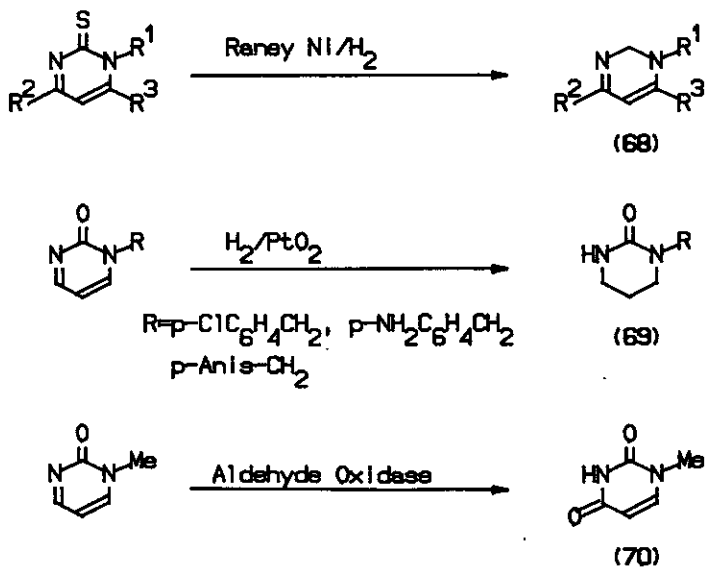
V Miscellaneous Reactions

Besides reactions described above, some interesting reactions have been reported. 5-Aryl-1-methyl-2(1H)-pyrimidinones underwent abnormal demethylation under phosphorous oxychloride-phosphorous pentachloride condition to give 2-chloropyrimidines (66).[102,103] 1,4,6-Trisubstituted 2(1H)-pyrimidinones (15) were easily converted into the corresponding 2(1H)-pyrimidinethiones (16) in high yields by reacting with 2,4-bis(p-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide (Lawesson's reagent).[104] On the contrary, 2(1H)-pyrimidinethiones (16) were converted into the corresponding 2(1H)-pyrimidinones (15) by the treatment with sodium hydroxide in ethanol.[62] The treatment of 4-substituted 1-amino-2(1H)-pyrimidinethiones with acyl halides yielded the ring fused products, pyrimidinothiadiazolium salts (67).[45] (Scheme 16)



Scheme 16

1,4,6-Trisubstituted 2(1H)-pyrimidinethiones were desulfurized with Raney nickel under hydrogen atmosphere to give novel 1,2-dihydropyrimidines (68).[76,77] The hydrogenation of 1-(p-substituted)benzyl-2(1H)-pyrimidinones in the presence of platinum oxide afforded the corresponding tetrahydroderivatives (69) in high yields.[49,50] Further, small scale oxidation of 1-methyl-2(1H)-pyrimidinone to 1-methyluracil (70) was achieved by using immobilized rabbit liver aldehyde oxidase.[105] (Scheme 17)



Scheme 17

VI Conclusion

Unsymmetrical N-substituted 2(1H)-pyrimidinones and pyrimidinethiones bearing various functional groups have become accessible as a result of the development of some excellent synthetic methods. In the case of ring transformation, nucleophiles such as active methylene compounds, amines, and hydroxylamine regioselectively attack C-6 carbon of the pyrimidine ring. Therefore N-substituted 2(1H)-pyrimidinones and pyrimidinethiones are useful intermediates for the regioselective synthesis of heterocycles having various functional groups. The photochemical reaction also provides a useful means of synthesizing chain organic compounds as well as heterocycles. Furthermore the synthetic utility of three types of reduced 2(1H)-pyrimidinones and pyrimidinethiones obtained selectively has scarcely unexplored. The authors expect rapid progress to be made in this field in the future.

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