SYNTHESIS OF PYRIMIDINE DERIVATIVES AND THEIR RELATED COMPOUNDS USING KETENE DITHIOACETALS

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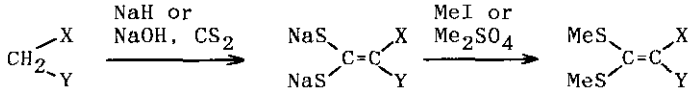
Abstract——Ketene dithioacetals bearing electron-withdrawing groups are useful and versatile reagents for the synthesis of pyrimidine derivatives. This review article describes the synthetic usefulness and importance of ketene dithioacetals in the preparation of pyrimidines and fused pyrimidine derivatives.

CONTENTS

1. INOTRODUCTION

Ketene dithioacetals bearing electron-withdrawing groups are versatile reagents for the synthesis of heterocycles and are extensively used.[1-31] In general, the ketene dithioacetals are obtained by the reaction of the corresponding active methylene compounds with carbon disulfide in the presence of a base followed by the alkylation with alkylating reagents such as methyl iodide or dimethyl sulfate. (Scheme 1) Among these compounds, ketene dithioacetals bearing the cyano or alkoxycarbonyl group at the β-position are extremely interesting electrophilic reagents for the introduction of not only an ethenyl group or an acrylate moiety into amines, active methylene compounds, and aromatic compounds but also three or two carbon units into the ring of heterocyclic compounds. Despite numerous reports concerning the application of these reagents to the synthesis of heterocycles, to our knowledge, there are no review articles to be reported. This review primarily describes the application of ketene dithioacetals to the synthesis of pyrimidine derivatives. Major emphasis will be placed on the results obtained in our own laboratory, along with additional results reported by the other groups. Ketene dithioacetals are also versatile reagents for the preparation of pyrimidine derivatives similar to ethoxymethylene compounds.[32-50]



1 2 3

	X	Y	Ref.
3a	CN	CN	1,2
b	CN	$SO_2C_6H_5$	3,4
c	CN	SO_2Me	4
d	CN	CO_2Me	1
e	CN	COC_6H_5	34
f	CO_2Me	CO_2Me	1
g	H	NO_2	6,20
h	H	COC_6H_5	7
i	H	$COC_6H_4Cl(p)$	7
j	H	$COC_6H_4Br(p)$	7
k	H	$COC_6H_4Me(p)$	7,9
l	H	2-furyl	7
m	$-COC_6H_4CO-$		15

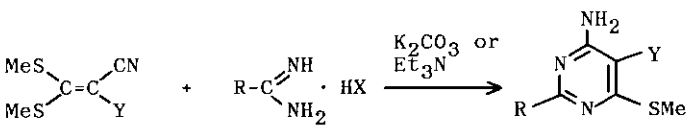
Scheme 1

2. SYNTHESIS OF PYRIMIDINES

Pyrimidine derivatives, which constitute a partial structure of purine bases and many biologically active compounds, are involved widely in living organisms and have attracted much attention from the viewpoint of the medicinal chemistry.[51-54] The soporific and hypnotic barbiturates and a number of antibacterial and antimalarial drugs also contain pyrimidine ring. Since the direct introduction of some specified substituents into the pyrimidine nucleus is not always easy, efforts directed to the construction of the ring bearing useful functionalized groups in the first step have been devoted.

2.1 Reactions of Ketene Dithioacetals with Amidines

In 1958, Middleton and Engelhardt have first reported the synthesis of 2-phenylpyrimidine derivative (**5a**) by the reaction of **3a** with benzamidine hydrochloride in the presence of sodium methoxide in methanol.[55] Recently, syntheses of pyrimidine derivatives using α-oxoketene dithioacetals have briefly reviewed.[21] We have recently found that the synthesis of pyrimidines is generally attained by the condensation reaction of ketene dithioacetals with amidine derivatives in the presence of an appropriate base.[56,57] (Scheme 2) In a similar manner, Augustin et al. have reported independently the synthesis of 6-amino-4-methylthio-5-phenylsulfonylpyrimidines by the condensation of sulfonylketene dithioacetals with amidine derivatives in the presence of a base.[3]



3a,b **4a-e** **5a-g**

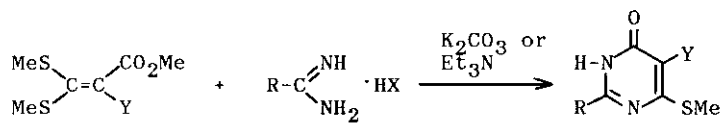
3a: Y=CN
b: Y=$SO_2C_6H_5$

	R	HX
4a	C_6H_5	HCl
b	Me	HCl
c	SMe	$1/2 \cdot H_2SO_4$
d	NH_2	$1/2 \cdot H_2CO_3$
e	$SCH_2C_6H_5$	HCl
f	SCH_2CN	HCl

	R	Y	Yield(%)
5a	C_6H_5	CN	55
b	Me	CN	77
c	SMe	CN	38
d	NH_2	CN	64
e	Me	$SO_2C_6H_5$	45
f	$SCH_2C_6H_5$	$SO_2C_6H_5$	34

Scheme 2

The reaction of **3d,f** with amidines (**4a-d, f**) also affords 6-substituted pyrimidine derivatives (**6a-e**) by the cyclization of methoxycarbonyl group and the amino group. Compound **6f** is prepared from **3d** and **4d** in good yields.[58] (Scheme 3)



3d,f **4a-d, f** **6a-f**

3d: Y=CN
f: Y=CO_2Me

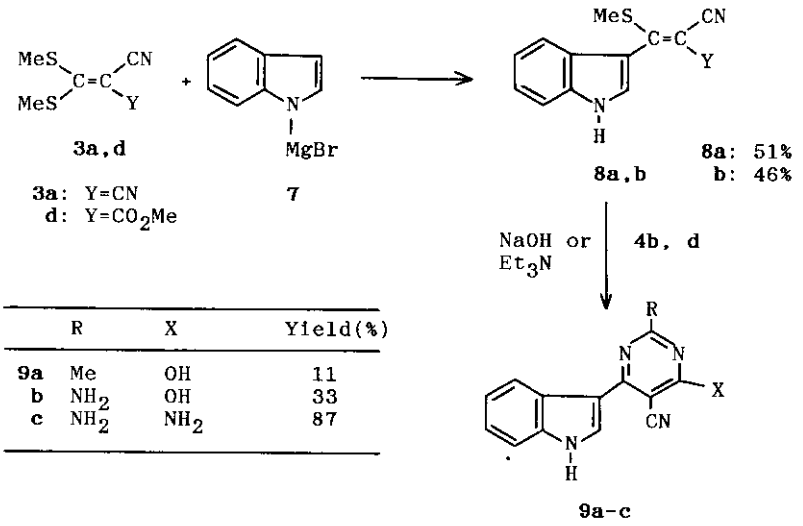
4a: R=C_6H_5, HX=HCl
b: R=Me, HX=HCl
c: R=SMe, HX=1/2·H_2SO_4
d: R=NH_2, HX=1/2·H_2CO_3
f: R=SCH_2CN, HX=HCl

	R	Y	Yield(%)
6a	C_6H_5	CN	55
b	Me	CN	77
c	SMe	CN	56
d	Me	CO_2Me	34
e	$SCH_2C_6H_5$	CN	82
f	NH_2	CN	67

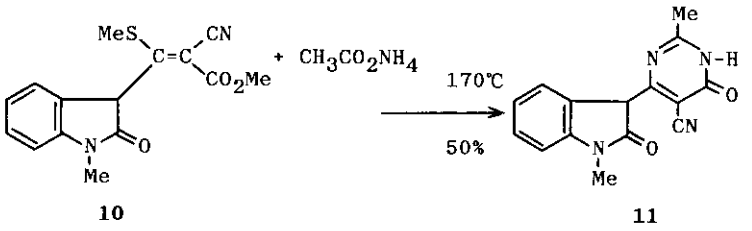
Scheme 3

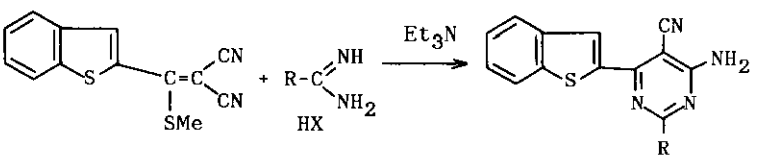
It is known as one of the most important characteristics in the reactivities of ketene dithioacetals that the displacement of one or two methylthio groups with two different nucleophiles can be achieved stepwise or at the same time under the appropriate conditions.

3-Indoleacrylate derivatives (**8a,b**), which are obtained by the reaction of indolylmagnesium bromide (**7**) with the ketene dithioacetals (**3a,d**), smoothly condens with amidine compounds (**4b,d**) to give the corresponding 4-(3-indolyl)-pyrimidine derivatives (**9a-c**).[59] 4-(1-Methyloxyindol-3-yl)pyrimidine derivative (**11**) is prepared by reaction of **10** with ammonium acetate at 170 ℃ in 50% yields.[60] Compound **12** also reacts with amidine compounds (**4b-d**) in the presence of a base like potassium carbonate to give the corresponding pyrimidine derivatives (**13a-c**).[61] (Scheme 4)



	R	X	Yield(%)
9a	Me	OH	11
b	NH_2	OH	33
c	NH_2	NH_2	87

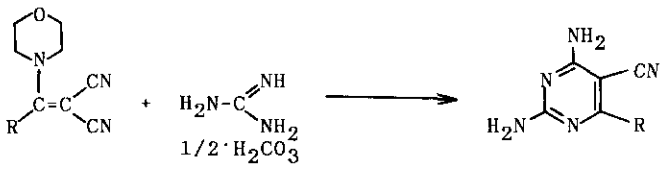




		Yield(%)
4b: R=Me, HX=HCl	**13a**: R=Me	57
c: R=SMe, HX=1/2·H_2SO_4	**b**: R=SMe	64
d: R=NH_2, HX=1/2·H_2CO_3	**c**: R=NH_2	71

Scheme 4

Recently, we have reported that polarized ethylenes(**14a-f**), prepared by the reaction of thioamide or dithiocarboxylate derivatives with tetracyanoethylene oxide in good yields, are smoothly reacted with guanidine carbonate (**4d**) on heating at 200 ℃ for 2 h to give the corresponding 2,4-diaminopyrimidine-5-carbonitrile derivatives (**15a-f**) in 52-90% yields.[62](Scheme 5)



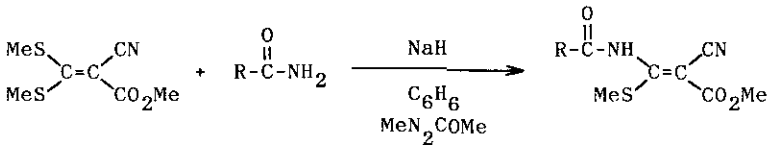
14a-f **4d** **15a-f**

	R	Yield(%)
15a	C_6H_5	85
b	$C_6H_4OMe(p)$	83
c	$C_6H_4Cl(p)$	90
d	$C_6H_4OMe(o)$	70
e	2-thienyl	71
f	$CH_2C_6H_5$	52

Scheme 5

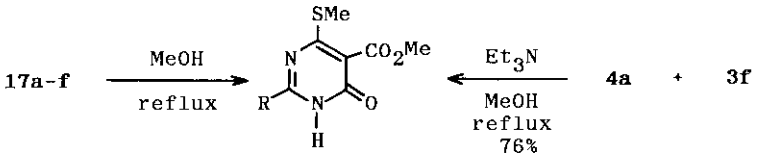
2.2 Reactions of Ketene Dithioacetals with Amides

In spite of numerous reactions of ketene dithioacetals with nucleophiles such as amines or active methylene compounds, to our knowledge, the reaction with carboxamides directed to the synthesis of heterocycles has been unknown.[57] The reaction of **3d** with the carboxamides (**16a-g**) in the presence of sodium hydride in a mixture of benzene and N,N-dimethylacetamide (1:1) at room temperature for 30 h gives methyl 3-benzoyl- or aroyl-amino-2-cyano-3-(methylthio)acrylate (**17a-f**) in moderate yield. The resulting **17a-f** are readily converted to methyl 3,4-dihydro-6-methylthio-4-oxo-2-phenylpyrimidine-5-carboxylate (**18a-f**) at reflux in methanol in good yields. Compound **18a** is alternatively prepared by the reaction of **3f** with **4a** in good yield. (Scheme 6) The reaction mechanism is shown in Scheme 7.[57]



3d **16a-g** **17a-g**

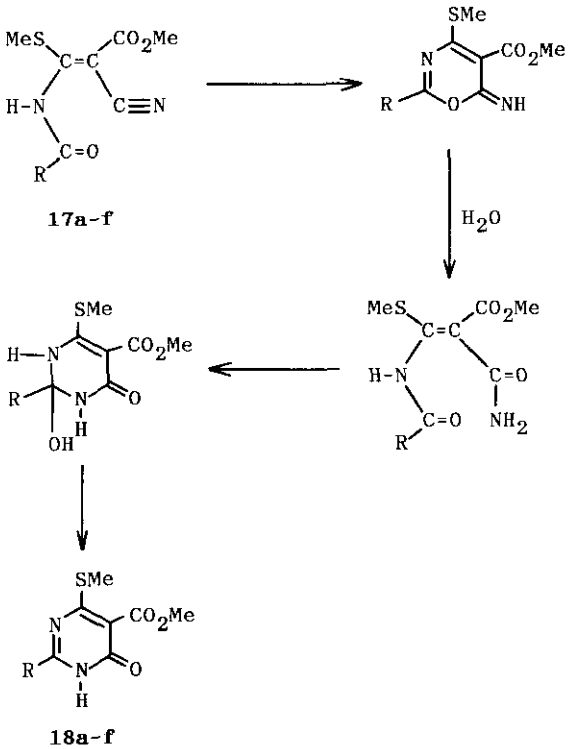
	R	Yield(%)
17a	C_6H_5	76
b	$C_6H_4NO_2(p)$	60
c	$C_6H_4Me(p)$	64
d	$C_6H_4OMe(p)$	39
e	$CH{=}CHC_6H_5$	73
f	CH_2Cl	40



18a-f

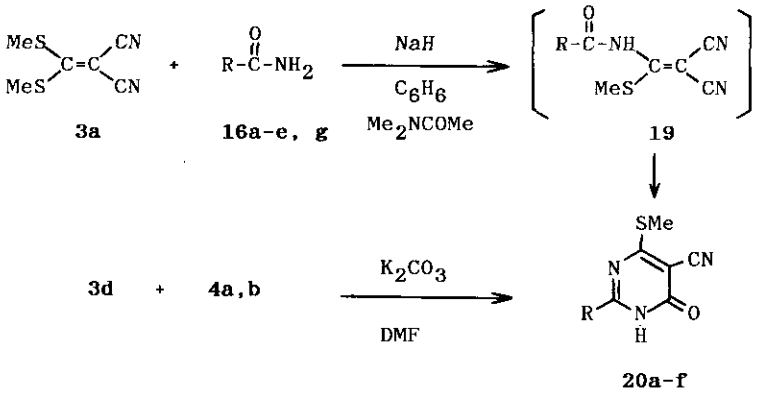
	R	Yield(%)
18a	C_6H_5	90
b	$C_6H_4NO_2$	96
c	$C_6H_4Me(p)$	98
d	$C_6H_4Me(p)$	95
e	$CH{=}CHC_6H_5$	91
f	CH_2Cl	94

Scheme 6



Scheme 7

Moreover, the reaction of **3a** with carboxamides (**16a-e,g**) gives directly the corresponding pyrimidine-5-carbonitriles (**20a-f**) under the same conditions as that described for **17a**. In this reaction, the corresponding intermediates **19** can not be isolated. Compounds **20a** and **20f** are also prepared by the reaction of **3d** with benzamidine hydrochloride (**4a**) and acetamidine hydrochloride (**4b**) in the presence of potassium carbonate in N,N-dimethylformamide(DMF) in 89 and 77% yields, respectively.[57] (Scheme 8)

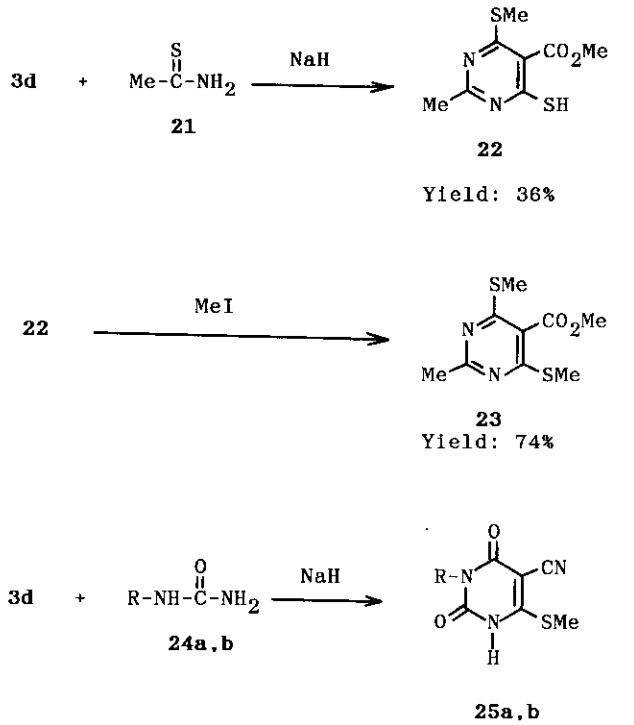


	R	Yield(%)
20a	C_6H_5	57(89)*
b	$C_6H_4NO_2$(p)	33
c	C_6H_4Me(p)	32
d	C_6H_4OMe(p)	30
e	$CH{=}CHC_6H_5$	35
f	Me	18(77)*

* from **3a** and **4a,b**.

Scheme 8

The ketene dithioacetal (**3d**) also reacts with thioacetamide (**21**) followed by the cyclization to yield methyl 4-mercapto-2-methyl-6-methylthiopyrimidine-5-carboxylate (**22**) which could be readily converted to methyl 2-methyl-4,6-bis(methylthio)pyrimidine-5-carboxylate (**23**) by methylation with methyl iodide in good yield. The reaction of **3d** with urea (**24a**) or N-phenylurea (**24b**) affords the corresponding 6-methylthiouracil-5-carbonitriles (**25a,b**). In this case, the cyclization of the methoxycarbonyl group of ketene dithioacetals with the carbamoyl group of urea occurs, and the corresponding uracil derivatives (**25**) are obtained.[57] (Scheme 9)



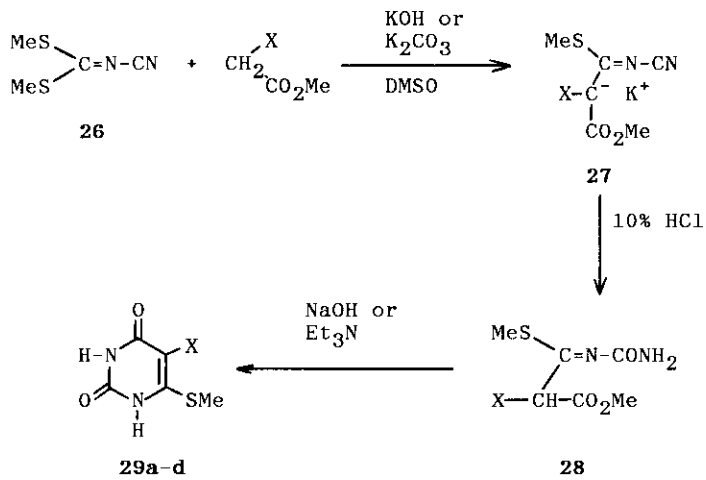
Scheme 9

2.3 Reactions of with N-[Bis(methylthio)methylene]cyanamide with Active Methylene Compounds

N-[Bis(methylthio)methylene]cyanamide derivatives are important and versatile reagents which have been extensively utilized in the synthesis of biologically active heterocyclic compounds.[63,64] Among those compounds, N-[bis(methylthio)-methylene]cyanamide (**26**) is an extremely interesting electrophilic reagent for the introduction of not only an aminomethylene group to amines and active methylene compounds but also a C=N-C=N unit in the synthesis of heterocyclic compounds.[64-69]

Compound **26** is allowed to react with various types of active methylene compounds (methyl cyanoacetate, dimethyl malonate, ethyl acetoacetate, and ethyl phenyl-acetate) at room temperature in the presence of potassium hydroxide or potassium carbonate in dimethyl sulfoxide(DMSO) to give the corresponding potassium salts

(**27**) which are easily converted to the corresponding ureas (**28**). Treatment of these ureas (**28**) with 10% sodium hydroxide or triethylamine gives the expected uracil derivatives (**29a-d**).[70] (Scheme 10)



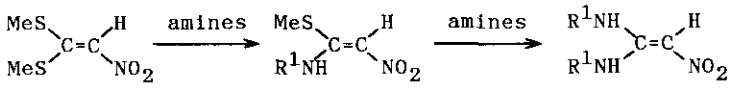
	X	Yield(%)
29a	CN	80
b	CO_2Me	75
c	COMe	15
d	C_6H_5	31

Scheme 10

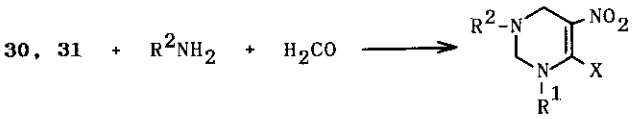
2.4 Double Mannich Reactions

Nitroenamine derivatives (**30**) which are prepared by the reaction of 1-nitro-2,2-bis(methylthio)ethylene (**3g**) with amines have been found to be of great utility in the synthesis of heterocyclic compounds.[20]

We have demonstrated the double Mannich reaction of **30** or **31** with formaldehyde and primary amines (benzylamine, methylamine, and aniline) to give the corresponding 1,2,3,6-tetrahydropyrimidine derivatives (**32a-k**) in good yields.[71] (Scheme 11)



3g **30** **31**



32a-k

	R^1	R^2	X	Yield(%)
32a	C_6H_5	C_6H_5	SMe	75
b	$C_6H_4OMe(p)$	$CH_2C_6H_5$	SMe	84
c	$C_6H_4Me(m)$	$CH_2C_6H_5$	SMe	65
d	$C_6H_3Cl_2(3,4)$	$CH_2C_6H_5$	SMe	63
e	C_6H_5	Me	NHC_6H_5	97
f	$C_6H_4OMe(p)$	Me	$NHC_6H_4OMe(p)$	71
g	$C_6H_4Me(m)$	Me	$NHC_6H_4Me(m)$	98
h	$C_6H_4Br(p)$	Me	$NHC_6H_4Br(p)$	72
i	$C_6H_3Cl_2(3,4)$	Me	$NHC_6H_3Cl_2(3,4)$	70
j	Me	Me	NHMe	63
k	$CH_2C_6H_5$	$CH_2C_6H_5$	$NHCH_2C_6H_5$	70

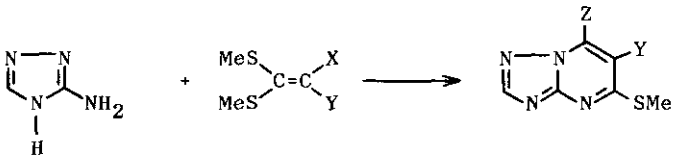
Scheme 11

3. CONSTRUCTION OF PYRIMIDINE-CONDENSED BICYCLIC RINGS

3.1 s-Triazolo[1,5-a]pyrimidines

Triazolo[1,5-a]pyrimidines are of considerable chemical and pharmacological importance.[72] In particular, trapymin, 7-(N,N-diethylamino)-5-methyl-s-triazolo-[1,5-a]pyrimidine, synthesized by Tenor and Ludwig, is used clinically as a coronary dilator.[73] Thus, we are interested in preparing functionalized triazolo[1,5-a]pyrimidines for the study as potential cardiovascular agents.

The reaction of 3-amino-4H-s-triazole (**33**) with ketene dithioacetals (**3a-f, h, m**) at 150 ℃ for 1.5 h gives the corresponding 5-methylthio-s-triazolo[1,2-a]-pyrimidine derivatives (***34a-h***) *in good yields*.[74] (*Scheme* 12)



33 **3a-f, h, m** **34a-h**

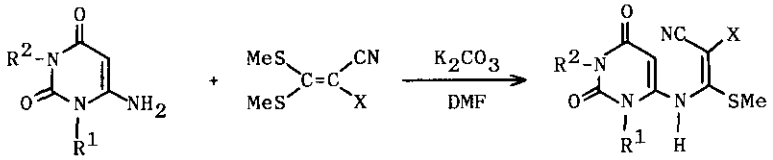
	Y	Z	Yield(%)
34a	CN	NH_2	70
b	$SO_2C_6H_5$	NH_2	94
c	SO_2Me	NH_2	92
d	CN	OH	83
e	CN	C_6H_5	87
f	CO_2Me	OH	83
g	H	C_6H_5	55
h	COC_6H_4CO		85

Scheme 12

3.2 Pyrido[2,3-d]pyrimidines

Enaminones are very useful and versatile compounds in organic synthesis. 6-Aminouracil derivatives involve the enaminone skeleton.[75] The reaction of 1,3-disubstituted 6-aminouracil (**35a,b**) with **3b** in the presence of potassium carbonate in DMF at 100 ℃ for 5 h gives only displacement products (**36a,b**) in good yields. Similarly, the reaction of **35a** with **3d** afforded the corresponding **36c**. These products (**36a-c**) at about 200 ℃ in diphenyl ether give the corresponding cyclized products, 5-amino-7-methylthiopyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione derivatives (**37a-c**) in good yields by the cyclization of the cyano group at the 5-position in uracil. When compounds **35a,b** react with **3a** in the presence of potassium carbonate in DMF at 100℃ for 5 h, the corresponding fused pyrimidopyrimidine derivatives, 5-amino-6-cyano-7-methylthiopyrimido[2,3-d]pyrimidine-2,4(1H,3H)-diones (**38a,b**), are obtained in 60 and 56% yields, respectively.[76]

Similarly, the reaction of **35a,b** with **3f** affords the corresponding desired products (**39a,b**), 5-hydroxy-6-methoxycarbonyl-7-methylthiopyrido[2,3-d]pyrimidine-2,4-(1H,3H)-dione derivatives in 48 and 20% yields, respectively.

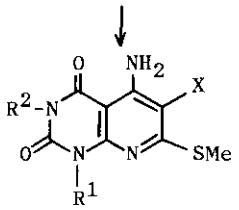


35a,b **3b,d** **36a-c**

a: $R^1=R^2=Me$
b: $R^1=C_6H_5$, $R^2=H$

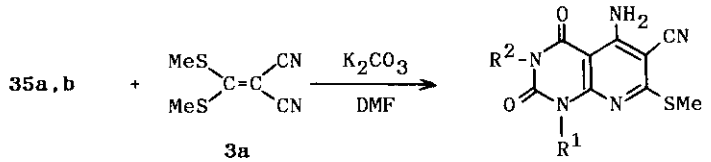
b: $X=SO_2C_6H_5$
d: $X=CO_2Me$

a: $R^1=R^2=Me$, $X=SO_2C_6H_5$
b: $R^1=R^2=Me$, $X=CO_2Me$
c: $R^1=C_6H_5$, $R^2=H$, $X=CO_2Me$

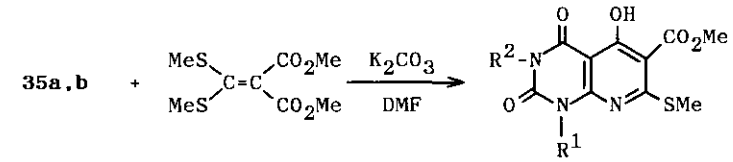


37a-c

	R^1	R^2	X	Yield(%)
37a	Me	Me	$SO_2C_6H_5$	46
b	Me	Me	CO_2Me	75
c	C_6H_5	H	CO_2Me	72



35a,b **3a** **38a,b**

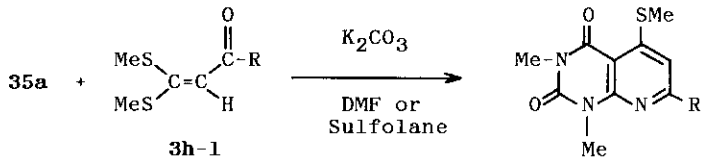


35a,b **3f** **39a,b**

	R^1	R^2	Yield(%)
38a	Me	Me	60
b	C_6H_5	H	56
39a	Me	Me	48
b	C_6H_5	H	20

Scheme 13

As pointed out by Junjappa et al.[11], α-oxoketene dithioacetals are very useful reagents for the preparation of heterocyclic compounds. The reaction of **35a** with **3h-l** in the presence of potassium carbonate at 150 ℃ in DMF or sulfolane gives the cyclized product, 7-aryl-1,3-dimethyl-5-methylthiopyrido[2,3-d]pyrimidine-2,4-(1H,3H)-diones (**40a-e**) in good yields. The above reaction is initiated by the condensation of the amino group of the pyrimidine ring with the carbonyl group in the ketene dithioacetal followed by the displacement of the methylthio group in the intermediates and the hydrogen atom at the 5-position of uracil.[78] (Scheme 14)



3h-l

40a-e

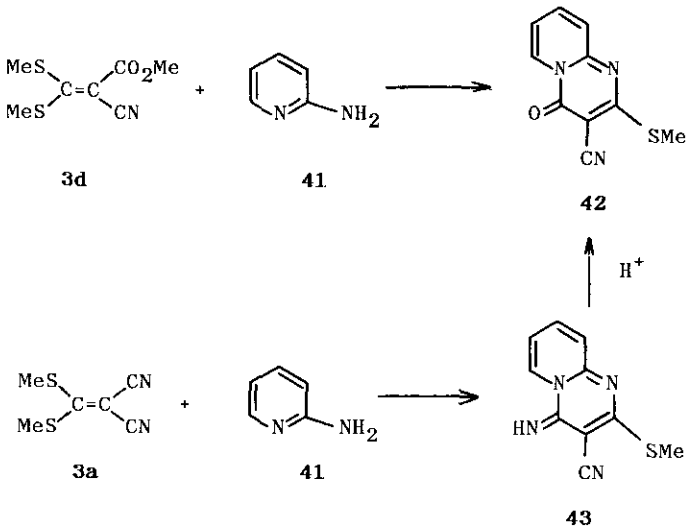
	R	Yield(%)
40a	C_6H_5	70
b	$C_6H_4Cl(p)$	85
c	$C_6H_4Br(p)$	85
d	$C_6H_4Me(p)$	40
e	2-furyl	42

Scheme 14

3.3 Pyrido[1,2-a]pyrimidines

Certain kinds of pyrido[1,2-a]pyrimidines attract much attention owing to their valuable pharmacological properties.[77] They are also used as synthetic intermediates or as additives to photographic materials and dyes.[79]

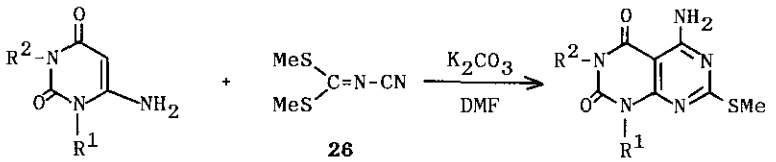
The reaction of 2-aminopyridine (**41**) with ketene dithioacetal (**3d**) leads to the 2-methylthio derivative (**42**), which is presumably formed via the addition-elimination mechanism.[80] Similarly, the reaction of **3a** with **41** affords 4-imino-4H-pyrido[1,2-a]pyrimidine derivative (**43**) which is readily converted to **42**.[79-81] (Scheme 15)



Scheme 15

3.4 Pyrimido[4,5-d]pyrimidines

The codensation of 6-aminouracils (**35a-c**) with N-[bis[methylthio)methylene]-cyanamide (**26**) in the presence of potassium carbonate in DMF at 100 ℃ for 5 h gives a fused pyrimidine, 5-amino-7-methylthiopyrimido[4,5-d]pyrimidine-2,4(1H,3H)-diones (**44a-c**).[78] (Scheme 16)



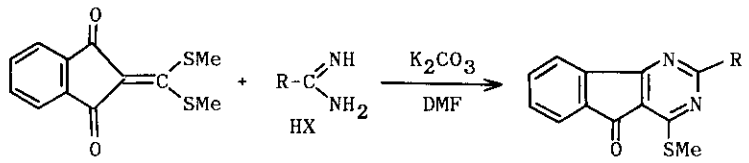
35a: $R^1=R^2=Me$
b: $R^1=C_6H_5$, $R^2=H$
c: $R^1C_6H_5$, $R^2=Me$

	R^1	R^2	Yield(%)
44a	Me	Me	73
b	C_6H_5	H	67
c	C_6H_5	Me	38

Scheme 16

4. CONSTRUCTION OF PYRIMIDINE-CONDESED TRICYCLIC RINGS

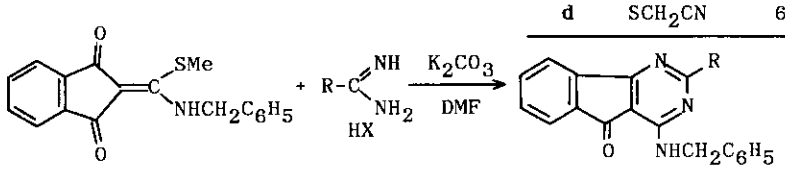
The reaction of 2-[bis(methylthio)methylene]-1,3-indanedione (**3m**) with amidine derivatives (**4b-d,f**) in the presence of potassium carbonate in DMF gives 2-substituted 4-methylthioindeno[1,2-d]pyrimidin-5-one (**45a-d**) in good yields. 4-Aminoindenopyrimidine derivatives (**47a-d** and **48a-d**) are also obtained by the reaction of **46a,b** with amidine derivatives (**4**).[82,83] (Scheme 17)



3p **4b-d,f** **45a-d**

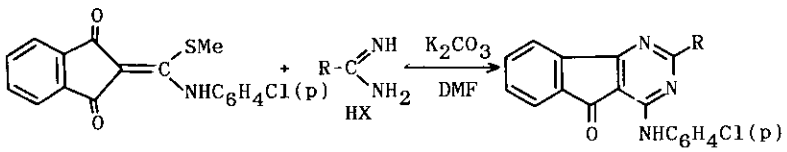
4b: R=Me, HX=HCl
c: R=SMe, HX=1/2·H_2SO_4
d: R=NH_2, HX=1/2·H_2CO_3
f: R=SCH_2CN, HX=HCl

	R	Yield(%)
45a	Me	74
b	SMe	89
c	NH_2	69
d	SCH_2CN	69



46a **4b-f** **47a-d**

	R	Yield(%)
47a	Me	74
b	SMe	89
c	NH_2	69
d	$SCH_2C_6H_5$	20
e	SCH_2CN	66



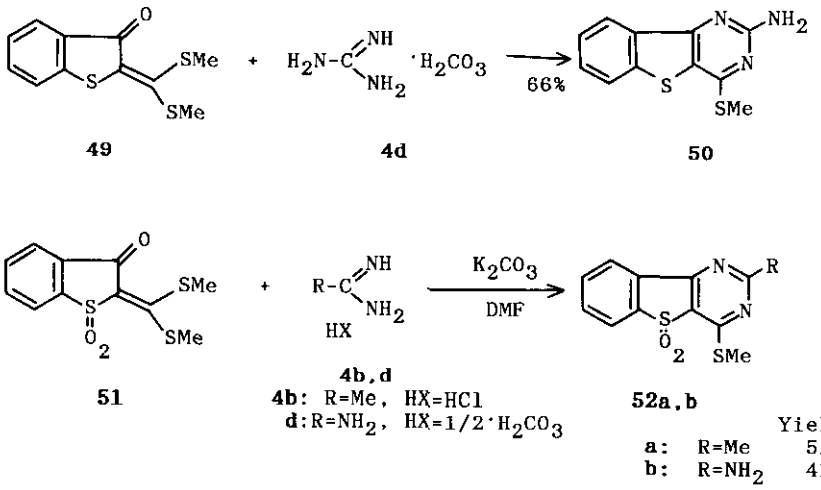
46b **4b-e** **48a-d**

	R	Yield(%)
48a	Me	77
b	SMe	93
c	NH_2	18
d	$SCH_2C_6H_5$	77

Scheme 17

*In a manner similar to ketene dithioacetals, bis(methylthio)methylene substitut-*ed heterocyclic compounds are attacked by nucleophilic reagents.[84-87] The replacement of either one or two methylthio groups attached to the same carbon atom occurs with such nucleophiles as amines or active methylene compounds. Therefore, these compounds are also very useful for the synthesis of the fused pyrimidine derivatives. However, the synthesis of pyrimidine derivatives using the above bis(methylthio)methylene heterocyclic compounds is not so many.

The reaction of **49** with guanidine carbonate as the amidine compound gives the corresponding fused pyrimidine derivative, pyrimido[4,3-d]benzo[b]thiophene (**50**) in good yield. Pyrimido[4,3-d]benzo[b]thiophene 5,5-dioxides (**52a,b**) are also obtained by the reaction of **51** with **4b** or **d**. (Scheme 18)



Scheme 18

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