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Review

β-Isothiocyanatoketones: A Convenient Source of Heterocyclic Compounds

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Summary. The preparation of β-isothiocyanatoketones and their reactions leading to formation of pyrimidine and bicyclic, tricyclic, tetracyclic, and pentacyclic heterocyclic compounds are reviewed. A few references concerning the rearrangement of heterocyclic compounds are also included. Some of the compounds reported have shown good antiinflammatory activity.

Keywords. Isothiocyanatoketones; Bi-, tri-, tetra-, and pentacyclic; Pyrimidines; Antiinflammatory.

Introduction

Isothiocyanatoketones are important reagents for the synthesis of various heterocyclic compounds. There is only scattered information available in literature about the synthetic utility of β-isothiocyanatoketones and thus an attempt was made to bring available information together in this review.

Synthesis of β-Isothiocyanatoketones

Several methods for the preparation of β-isothiocyanatoketones are available. Thus, *Bruson* [1] synthesized a number of ketothiocyanates **2a**–**2g** by addition of HSCN to α, β-unsaturated ketones (Scheme 1). 2-Methyl-2-thiocyano-4-pentanone (**3**) was synthesized by *Mathes* et al. [2] by following the reaction of Scheme 2.

Further examination of **3** by *Mathes* [3] using IR revealed quite conclusively that **3** was 2-methyl-2-isothiocyanato-4-pentanone and not 2-methyl-2-thiocyanato-4-pentanone. A number of β-isothiocyanatoketones **4a**–**4d** were synthesized by *Bhanot* et al. [4] (Scheme 3).

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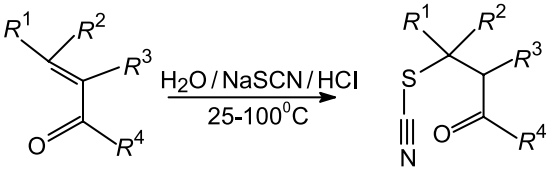
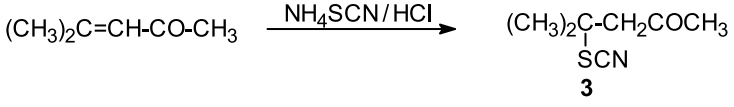


1 **2**

	R^1	R^2	R^3	R^4
2a:	CH_3	CH_3	H	CH_3
2b:	CH_3	CH_3	H	$Me_2C{=}CH$-
2c:	Et_2CH-	H	H	CH_3
2d:	n-C_4H_9-CH-Et	H	H	CH_3
2e:	R^1R^2-$(CH_2)_5$-		R^3R^4-$(CH_2)_4$-	
2f:	Et_2CH-	H	R^3R^4-$(CH_2)_4$-	
2g:	CH_3	R^2R^4-$CH_2C(CH_3)_2CH_2$-	H	

Scheme 1



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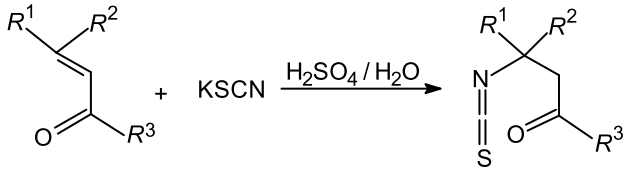
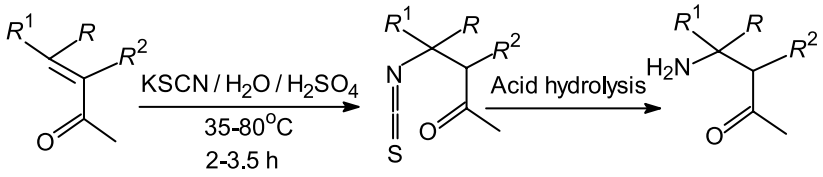
Scheme 2



	R^1	R^2	R^3
4a:	CH_3	CH_3	CH_3
4b:	C_2H_5	CH_3	C_2H_5
4c:	CH_3	CH_3	C_2H_5
4d:	CH_3	CH_3	C_6H_5

Scheme 3

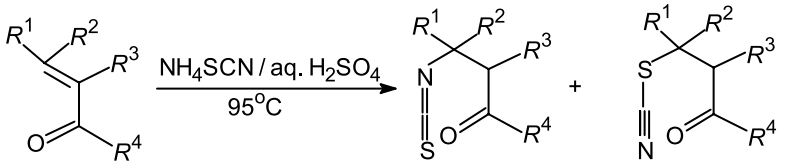


5a-5e **6a-6e**

	R	R^1	R^2
a:	H	H	CH_3
b:	H	H	H
c:	H	CH_3	H
d:	H	CH_3	CH_3
e:	H	*Ph*	H

Scheme 4

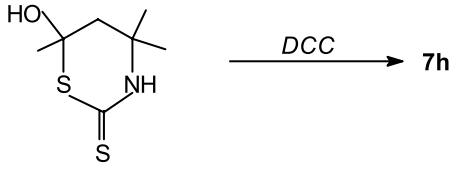
The β-isothiocyanato ketones [5, 6] **5a**–**5e** were synthesized by treating α,β-unsaturated ketones with $KSCN/H_2O/H_2SO_4$ at 35–80°C for 2–3.5 h. Acid hydrolysis of **5a**–**5e** gave aminoketones **6a**–**6e** (Scheme 4).



7a-7k **8a-8e**

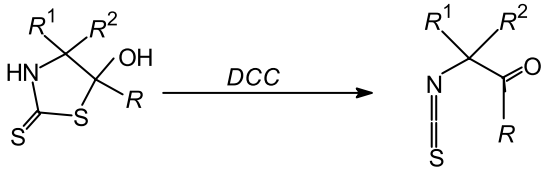
	R^1	R^2	R^3	R^4
a:	H	H	H	H
b:	H	H	CH_3	CH_3
c:	H	H	CH_3	H
d:	H	H	CH_3	C_2H_5
e:	H	H	H	CH_3
f:	H	CH_3	H	H
g:	H	CH_3	H	CH_3
h:	CH_3	CH_3	H	CH_3
i:	CH_3	CH_3	CH_3	CH_3
j:	CH_3	CH_3	CH_3	C_2H_5
k:	CH_3	CH_3	CH_3	*n-Pr*

Scheme 5



6

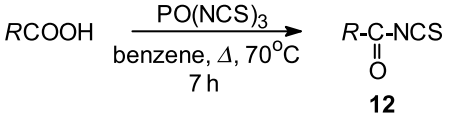
Scheme 6



10a-10f **11a-11f**

	R	R^1	R^2
a:	*Ph*	H	H
b:	*Ph*	CH_3	CH_3
c:	*Ph*	*Ph*	*Ph*
d:	*Ph*	*Ph*	H
e:	C*Me*$_3$	H	H
f:	CH_3	CH_3	CH_3

Scheme 7



R = C_6H_5, *o*-CH_3-C_6H_4-, *m*-CH_3-C_6H_4-, *p*-H_3CO-C_6H_4-, *p*-O_2N-C_6H_4-, C_6H_5CH=CH- , 2-thienyl, *etc.*

Scheme 8

Peretokin et al. [7] synthesized **7a**–**7k** by treating $R^1R^2C=CR^3COR^4$ with NH_4SCN in aqueous sulfuric acid at 95°C. As was evident from the IR, ^1H, and ^{13}C NMR spectra **7a**–**7e** were accompanied by thiocyanates **8a**–**8e** as minor products, however, compounds **7f**–**7k** (Scheme 5) were pure isothiocyanates only.

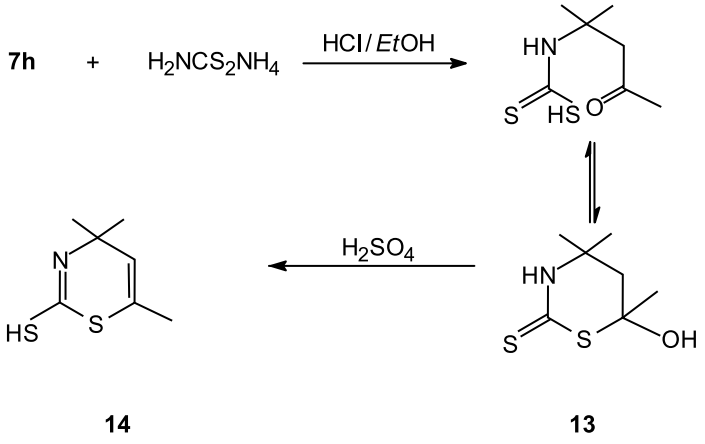
2-Methyl-2-isothiocyanato-4-pentanone (**7h**) was synthesized by cleavage of 6-hydroxyperhydro-1,3-thiazin-2-thione (**9**) with dicyclohexylcarbodiimide (*DCC*) [8] (Scheme 6). In addition, a number of 2-keto-isothiocyanates (**11a**–**11f**) were also synthesized by cleavage of hydroxythiazolidinethiones **10** with *DCC* [8] (Scheme 7).

Ladislav et al. [9] synthesized a number of acyl isothiocyanates (**12**) by reaction of carboxylic acids with phosphoryl isothiocyanate (Scheme 8). In the following pages use of β-isothiocyanatoketones for the synthesis of various targets is described.

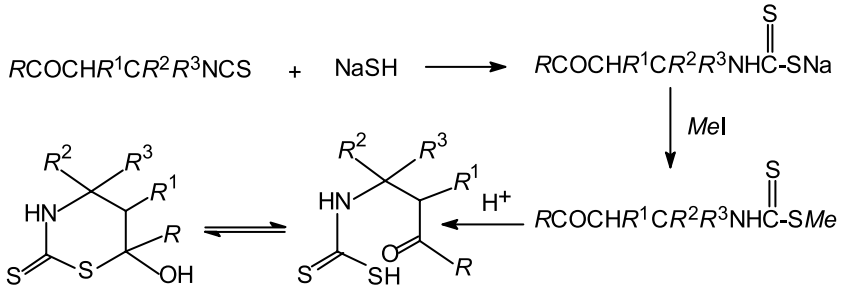
Synthesis of Monocyclic Derivatives

Condensation of 2-methyl-2-isothiocyanato-4-pentanone (**7h**) with $NH_2CS_2NH_4$ in presence of HCl and ethanol gave **13**, which on dehydration with H_2SO_4 gave 4,4,6-trimethyl-4*H*-1,3-thiazine-2-thiol (**14**) (Scheme 9) [10]. The thiazinethiones **15** were obtained [11] from $RCOCHR^1CR^2R^3NCS$ by the reaction sequence of Scheme 10.

Mathes et al. [2] synthesized a number of pyrmidine derivatives (**16**) by the reaction of RNH_2 with 2-methyl-2-thiocyano-4-pentanone under acidic conditions (Scheme 11). The same author further condensed amino carboxylic acids with 2-methyl-2-thiocyano-4-pentanone to give pyrimidine derivatives **17** (Scheme 12).

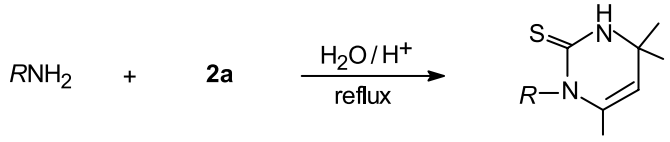


Scheme 9



	R	R^1	R^2	R^3
15a:	*Me*	H	H	H
15b:	*Et*	*Me*	*Me*	*Me*
15c:	$RR^1 = (CH_2)_4$		$R^2R^3 = (CH_2)_5$	

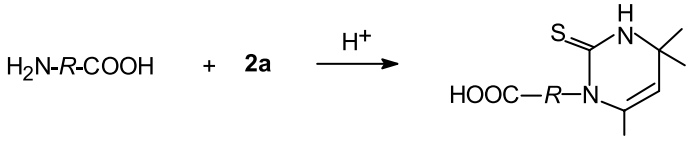
Scheme 10



16

R = H, *p*-tolyl, 2-naphthyl, $HOCH_2CH_2$-, $CH_3CH_2CH_2$-, cyclohexyl, *etc.*

Scheme 11

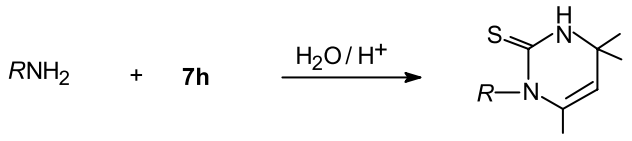


R = -CH_2-, -CH(-CH_3)-, -C_6H_4- **17**

Scheme 12

In 1953 *Mathes* et al. pointed out that **2a** used above [2, 12] was actually **7h** and he reported the synthesis of several other pyrimidine derivatives **18** by condensation of RNH_2 with **7h** in refluxing aqueous acidic medium [3] (Scheme 13).

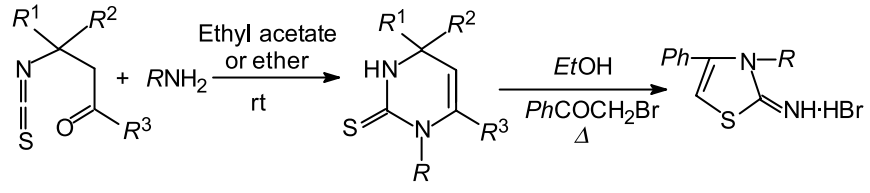
Several 2-mercapto pyrimidines **19** were synthesized by condensation of various amines with β-isothiocyanatoketones at room temperature using ether or ethylacetate as the solvent of reaction and then crystallizing the crude product from acetic acid. Condensation of **19** with ω-bromoacetophenone gave thiazoline derivatives **20** [4] (Scheme 14). A number of hexahydropyrimidine thiones **21** were synthesized as shown in Scheme 15 [5, 6]. *Zigeuner* et al. [13] synthesized pyrimidine derivatives **22** by heating an amine with β-isothiocyanatoketones in an inert solvent (Scheme 16).



18

R = H_2N-, anilino, -CH_3, -C_2H_5, *n*-butyl, allyl, 3-isopropoxypropyl, *p*-O_2N-C_6H_4-, 2,4-dichlorophenyl, *o*-HS-C_6H_4-, *p*-HO-C_6H_4-, *p*-H_3CO-C_6H_4-, *p*-acetylphenyl, benzyl, *etc*.

Scheme 13

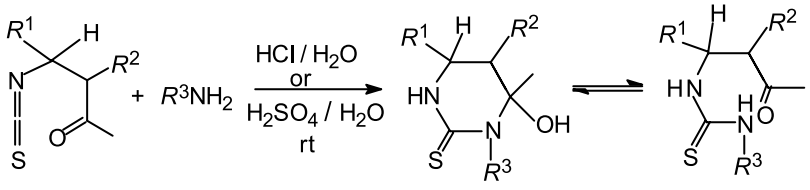


19 **20**

R = *Ph*, H, *p*-Cl-C_6H_4-

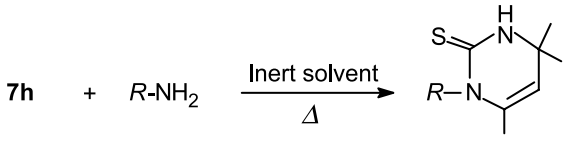
	R	R^1	R^2	R^3
a:	C_6H_5	CH_3	C_2H_5	C_2H_5
b:	H	CH_3	C_2H_5	C_2H_5
c:	C_6H_5	CH_3	CH_3	C_2H_5
d:	*p*-C_6H_4Cl	CH_3	CH_3	C_2H_5
e:	H	CH_3	CH_3	C_2H_5
f:	H	CH_3	CH_3	C_6H_5

Scheme 14



	R^1	R^2	R^3
21a:	H	*Me*	H
21b:	H	*Me*	*Me*
21c:	H	*Me*	*Et*
21d:	H	*Me*	*n-Pr*
21e:	H	*Me*	*Ph*
21f:	H	*Me*	*Ph*-CH_2-
21g:	H	H	*Me*
21h:	H	H	Ph
21i:	*Me*	*Me*	*Me*

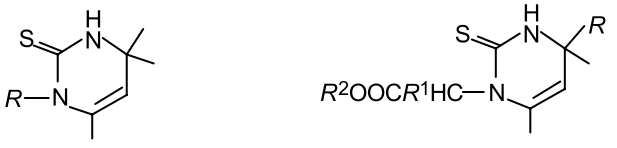
Scheme 15



R = *Ph*, CH_2=CH-CH_2-, *Me*, *Ph*CH_2-, *n-Bu*-, Me_2CHCH_2-, $NCCH_2CH_2$-, *Ph*CH_2CH_2-, *p*-HO-C_6H_4-, *p*-HS-C_6H_4-, *p*-HO-$C_6H_4CH_2CH_2$-

Scheme 16

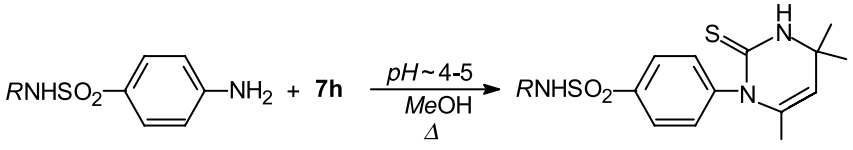
Bebikh et al. [14, 15] condensed *n*-pentylamine and 3-(decyloxy)propylamine with **7h** to obtain pyrimidine derivatives **23a** and **23b**, which are useful as antiwear and antiscuff additives for lubricating oils. α-(2-Thiono-1,2,3,4-tetrahydropyrimid-1-yl)-carboxylic acids and esters **24** were synthesized by condensation of $H_2NCHR^1COOR^2$ with *Me*$COCH_2C$*RMe*NCS in 39–64% yield [16] (Scheme 17). A number of sulphadrugs were condensed with **7h** by refluxing in methanol at *pH* ~ 4–5 to give pyrimidine derivatives **25a**–**25f** [17] (Scheme 18). All the



	R
23a:	-$(CH_2)_4CH_3$
23b:	-$(CH_2)_3OC_{10}H_{21}$

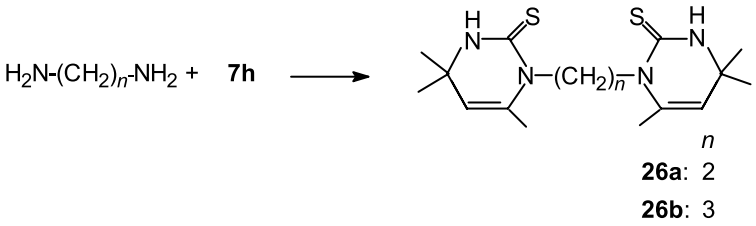
	R	R^1	R^2
24a:	H	*Me*	H
24b:	H	-CHMe_2	H
24c:	H	-CH_2CHMe_2	H
24d:	H	-CH*MeEt*	H
24e:	H	-CH_2*Ph*	H
24f:	CH_3	*Me*	*Et*
24g:	CH_3	-CHMe_2	*Et*

Scheme 17



	R		*R*
25a:		**25b**:	
25c:		**25d**:	
25e:	CH_3CO-	**25f**:	H

Scheme 18

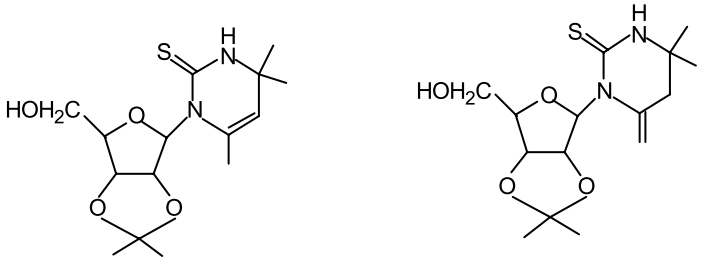


Scheme 19

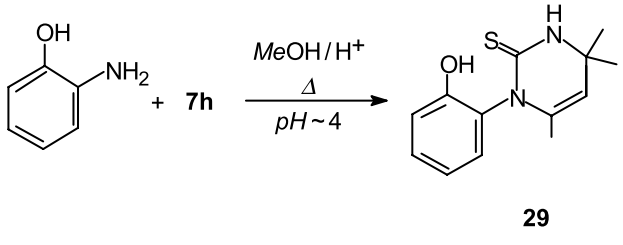
compounds were screened for anticancer [18, 19], antiinflammatory [20], and analgesic activities [21] and several of these compounds showed mild analgesic activity. 1,2-Diaminoethane and 1,3-diaminopropane on condensation with **7h** gave pyrimidine derivatives **26** [22] (Scheme 19).

Shutalev et al. [23] synthesized *N*-glycosides **27** and **28** by the reaction of 2,3-*O*-isopropylideneribofuranosylamine tosylate with 4-methyl-4-isothiocyanato-2-pentanone in dry pyridine. The ratio of **27:28** was 3:7 but the yield was only 10% (Scheme 20).

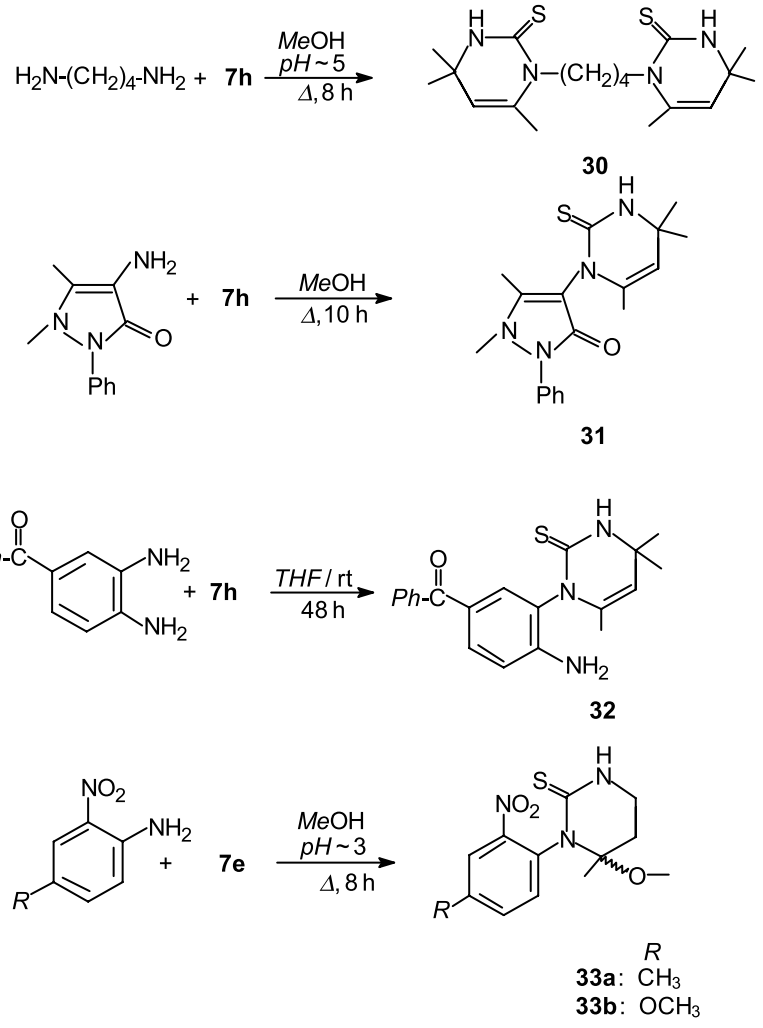
Condensation of *o*-aminophenol with **7h** at $pH \sim 4$ by refluxing in methanol gave the pyrimidine derivative **29** [24] (Scheme 21). Several pyrimidine derivatives were synthesized by *Sondhi* et al. [25] (Scheme 22). Compounds **30** and **32** showed weak analgesic [21] and compounds **33a** and **33b** showed weak antiinflammatory activity [20]. Formation of pyrimidinethione **34** by refluxing 4-methyl-4-isothiocyanato-2-pentanone (**7h**) with acetic acid for 11 h is reported in literature. A mechanism of the formation of **34** has also been described [26] (Scheme 23). Synthesis of compounds **35** and **36** by condensation of 3-isothiocyanatobutanal with 2,3-diaminopyridine and 1,4-diaminobutane is reported in Ref. [27] (Scheme 24).



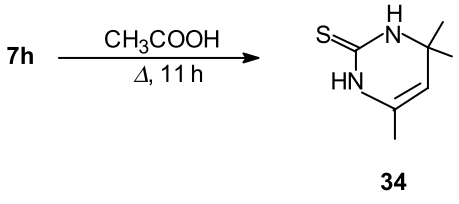
Scheme 20



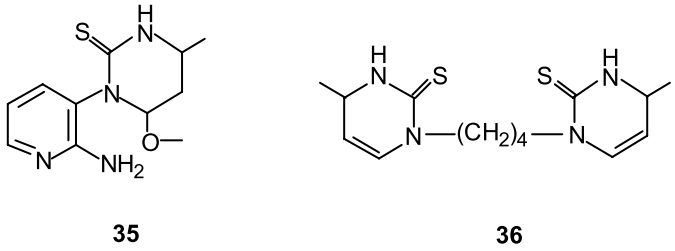
Scheme 21



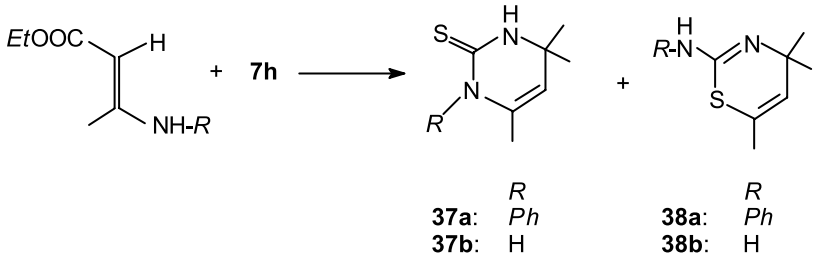
Scheme 22



Scheme 23



Scheme 24



Scheme 25

Singh et al. [28, 29] described the formation of 2-mercapto-3-phenyl-4,6,6-trimethyl-3,6-dihydropyrimidine (**37**) and 2-anilino-4,4,6-trimethyl-1,3-thiazine (**38**) as major and minor products of the reaction of ethyl β-anilinocrotonate with 4-methyl-4-isothiocyanato-2-pentanone (**7h**) (Scheme 25). When the solvent was changed from *n*-hexane, benzene, or toluene to ether, acetonitrile, butan-2-one, ethylacetate, or chloroform the major product **37** became the minor product and **38** became the major one. A number of pyrimidine derivatives having pyridine or pyrimidine derivatives as a substituent have been synthesized as given in Scheme 26 [30]. In case of **39**–**44** only pyrimidine derivatives and not tricyclic condensed pyrimidine derivatives were obtained, which is due to the inertness of the amino group ortho or para to the ring nitrogen. Compounds **39a**, **39b**, **41a**, **41b**, and **44** showed weak antiinflammatory and analgesic activities [20, 21]. Condensation of 2-aminopyridine with **7h** at room temperature gave the hydroxypyrimidine **45** and on refluxing at $pH \sim 4$ for 36 h gave the pyrimidine derivative **46** in poor yields [31] (Scheme 27).

A number of pyrimidine thiones **47** [32] have been synthesized by the cyclization of $CH_3COCH_2CMeRNCS$ with $R^1CONHNH_2$ (Scheme 28). *Hofmann* et al. [33] synthesized 1-(2-thiono-1,2,3,4-tetrahydro-1-pyrimidyl)thioureas **48** by condensation of $R^3COCHR^2CRR^1NCS$ with H_2NNR^4 $CSNH_2$ (Scheme 29). β-Isothiocyanatoketone **7h** reacted with substituted hydrazine in the presence of base to give seven membered heterocyclic compounds **49** [34, 35] whereas in absence of base, **50** was obtained [36] (Scheme 30).

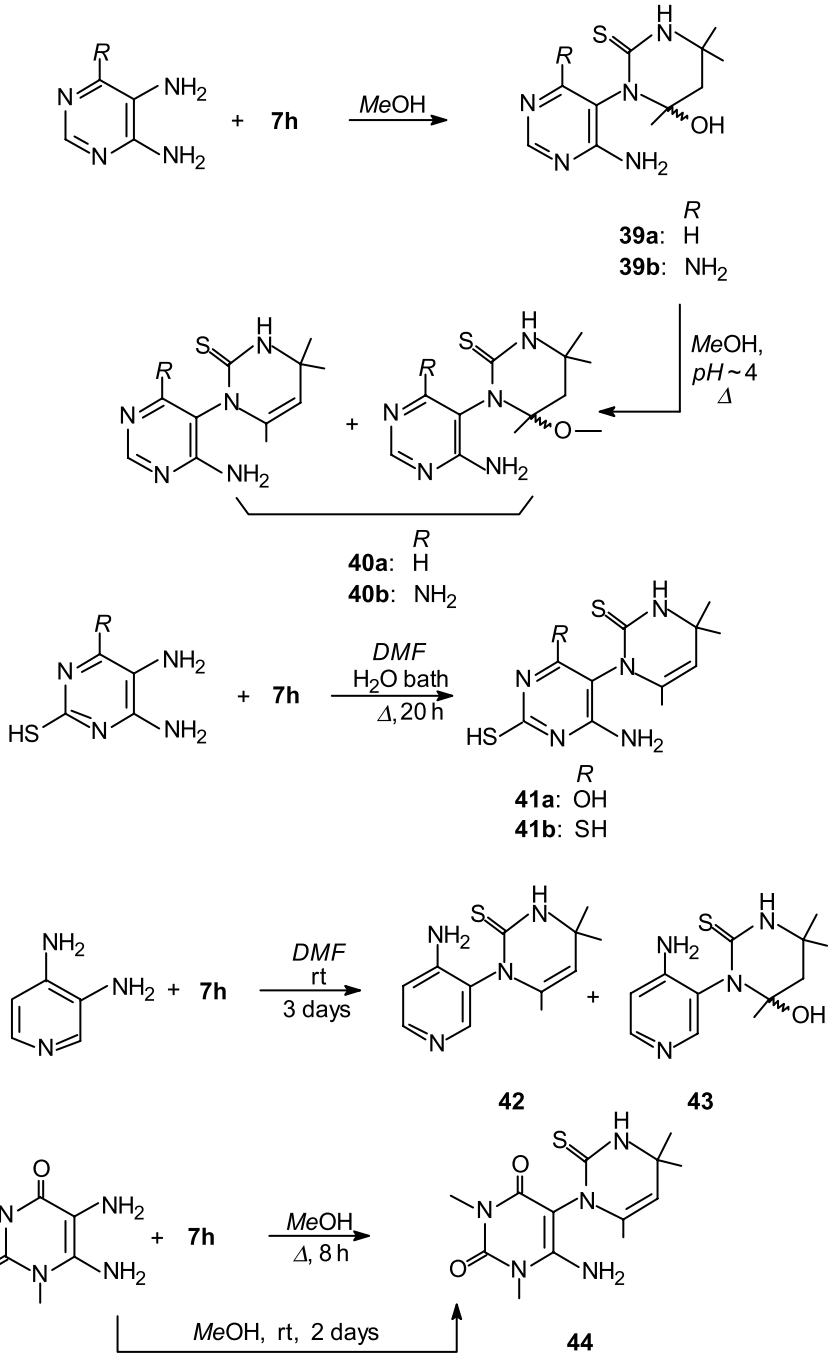
Neidlein et al. [37] synthesized a number of pyrimidine thiones **51** by treating $R^1COCHR^2CR^3R^4NCS$ with p-H_2NNHSO_2-C_6H_4-R (Scheme 31). He further synthesized [38] *S*-alkylated derivatives **52**, *N*-acylated derivatives **53**, and then converted **53** to the corresponding 2-oxo analogs by treatment with H_2O_2 (Scheme 32).

1,1′-Bis-(2-thioxopyrimidines) **56** were synthesized [39] by cyclocondensation of **7h** with **54** to give **55**, which undergoes dehydration by refluxing in *Et*OH with HCl to give **56**. Compound **56** can also be prepared by cyclocondensation of N_2H_4HCl with **7h** (Scheme 33).

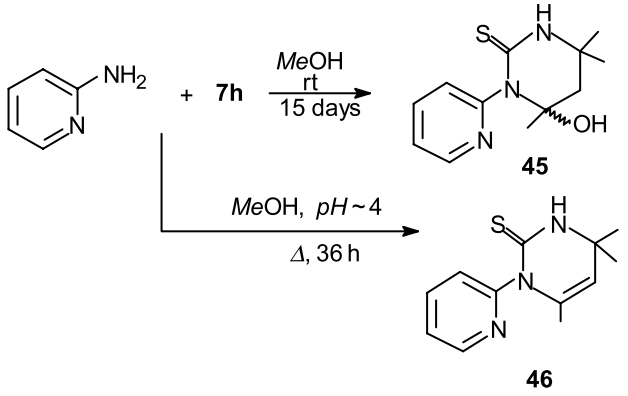
Condensation of glycine with 4-isothiocyanatobutan-2-one gave 3-(3-oxobutyl)-4-oxoimidazolidine-2-thione (**57**) and not the corresponding pyrimidine [40] (Scheme 34).

β-Isothiocyanatoketones $RCOCHR^1NCS$ on cyclization [8] gave oxazolines **58**. On condensation of $RCOCR^1R^2NCS$ ($R^2 = Me$, Ph) with amines imidazolidi-

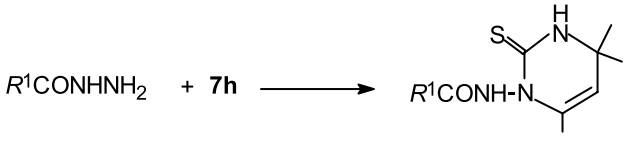
nethiones **59** were obtained, which could not be acetylated at the OH group, instead it was dehydrated endo- or exocyclically but acylated on NH (Scheme 35). $R^1COCR^2R^3NCS$ undergoes condensation with NH_2NH_2 to give



Scheme 26

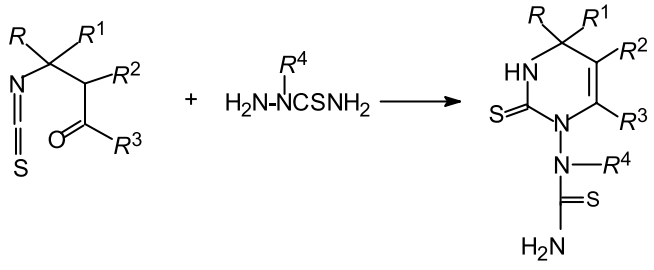


Scheme 27



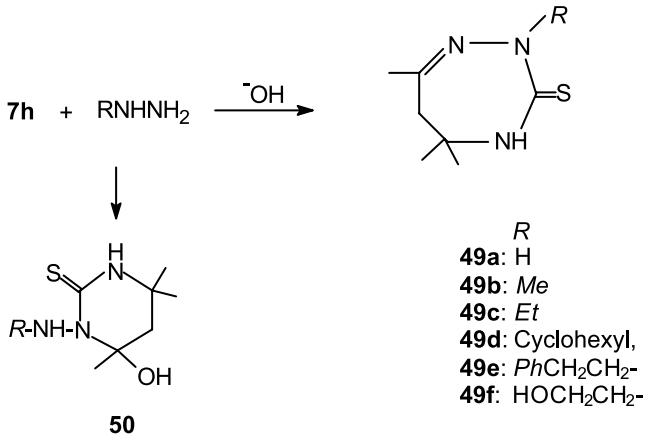
	R^1		R^1		R^1
47a:	*Me*	**47b**:	*Et*	**47c**:	*n-Pr*
47d:	*Ph*	**47e**:	*Ph*CH_2-	**47f**:	O_2N-C_6H_4-
47g:	ClC_6H_4-	**47h**:	HOC_6H_4,	**47i**:	*Me*OC_6H_4
47j:	*Ph*OCH_2-	**47k**:	$ClC_6H_4OCH_2$-, *etc.*		

Scheme 28

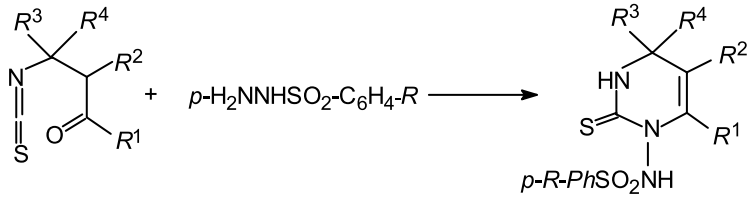


	R	R^1	R^2	R^3	R^4
48a:	H	*Me*	H	*Me*	H
48b:	*Me*	*Me*	H	*Me*	*Me*
48c:	RR^1 = -$(CH_2)_4$-		R^2R^3 = -$(CH_2)_3$-		H
48d:	RR^1 = -$(CH_2)_5$-		R^2R^3 = -$(CH_2)_4$-		H

Scheme 29



Scheme 30



	R	R^1	R^2	R^3	R^4
51a:	H	*Me*	H	*Me*	*Me*
51b:	*Me*	*Me*	*Me*	H	H
51c:	Cl	R^1R^2 = -$(CH_2)_3$-		R^3R^4 = -$(CH_2)_4$-	
51d:	CH_3ONH-	*Me*	H	*Me*	*Me*

Scheme 31

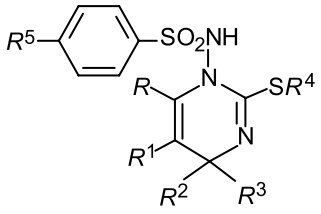
aminoimidazolidinethiones **60** or triazines **61** and with alcohols to give alkoxyoxazolidinethiones **62**. Reaction of *R*COCR^1R^2NCS with *Me*MgI gave 4,4,5,5-tetrasubstituted oxazolidinethiones **63** (Scheme 36).

Synthesis of Bicyclic Compounds

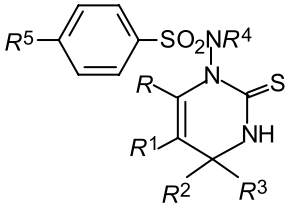
A number of bicyclic derivatives [22], *i.e.* imidazopyrimidine **64**, pyrimidopyrimidine **65**, oxazolopyrimidine **66**, and pyrimidooxazine **67**, have been synthesized as shown in Scheme 37.

Condensation of 4-isothiocyanatobutane-2-one (**7e**) with 2-aminoethanol, 2-aminoethanthiol, 1,2 ethanediamine, and 1,3-propanediamine under basic conditions provides the corresponding oxazolo-, thiazolo-, imidazolopyrimidines **68a**–**68c**, and pyrimidopyrimidine **69** (Scheme 38) [41, 42].

Condensation of 3-isothiocyanatobutanal (**7f**) with 2-aminoethanol, 2-mercaptoethylamine, 3-aminopropan-1-ol, and 1,3-propanediamine gave **70a**–**70b** and **71a**–**71b** as shown in Scheme 39 [42].

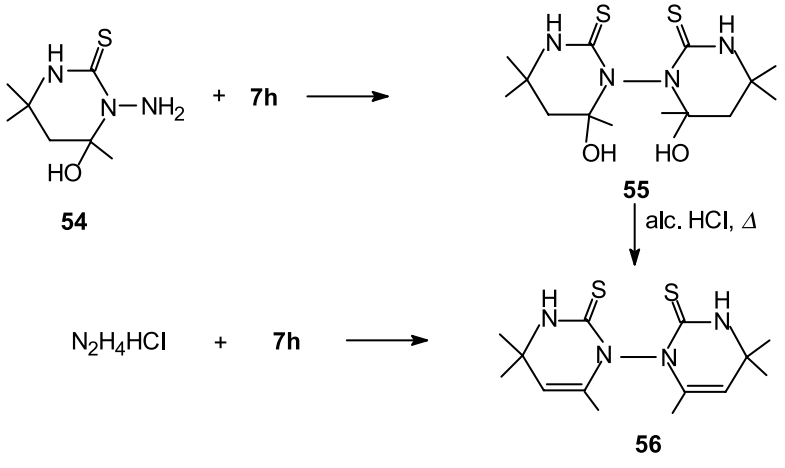


	R	R^1	R^2	R^3	R^4	R^5
52a:	*Me*	H	*Me*	*Me*	*Me*	*Me*
52b:	*Me*	H	*Me*	*Me*	CH_2COOH	*Me*
52c:	*Me*	H	*Me*	*Me*	CH_2COOEt	*Me*
52d:	*Me*	H	*Me*	*Me*	CH_2COOEt	H

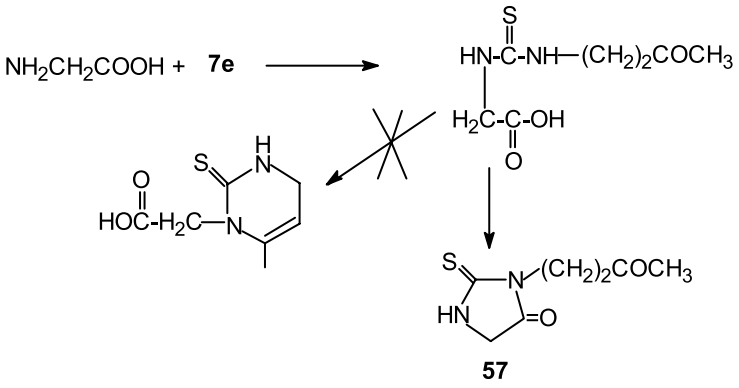


	R	R^1	R^2	R^3	R^4	R^5
53a:	*Me*	H	*Me*	*Me*	*Ac*	*Me*
53b:	$RR^1 = -(CH_2)_3-$		$R^2R^3 = -(CH_2)_4-$		*Ac*	*Me*
53c:	*Me*	H	*Me*	*Me*	$COCBrMe_2$	H
53d:	*Me*	H	*Me*	*Me*	$COCH_2CH_2Br$	H

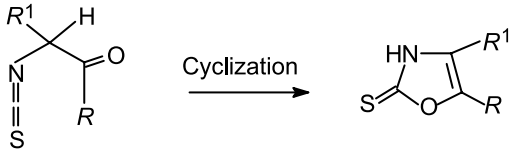
Scheme 32



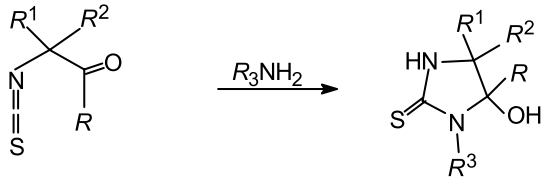
Scheme 33



Scheme 34



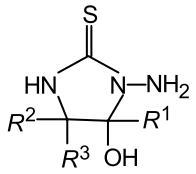
	R	R^1
58a:	*Ph*	H
58b:	*Ph*	*Me*
58c:	*Ph*	*Ph*
58d:	C*Me*$_3$	H



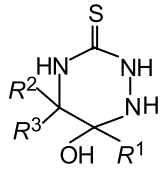
	R	R^1	R^2	R^3
59a:	CH_3	CH_3	CH_3	H
59b:	C_6H_5	CH_3	CH_3	H
59c:	CH_3	CH_3	CH_3	CH_3
59e:	C_6H_5	CH_3	CH_3	CH_3

Scheme 35

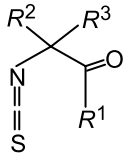
Condensation of 4-isothiocyanato-4-methyl-2-pentanone (**7h**) with 2-aminoethanol at $pH \sim 2$ gave oxazolopyrimidinethione **66** (Scheme 40). It showed 21% antiinflammatory activity at 100 mg/kg *p.o.* [24]. Condensation of **7h** with ethylenediamine at room temperature gave the pyrimidine derivative **72** whereas the same reaction at $pH \sim 5$ under reflux in methanol yielded the imidazolopyrimidine **64** (Scheme 41) [31]. Similarly, condensation of **7h** with 3-aminopropanol

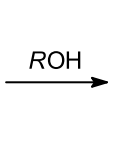


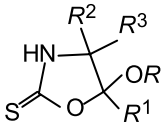
	R^1	R^2	R^3
60a:	*Me*	*Me*	*Me*
60b:	*Ph*	*Me*	*Me*

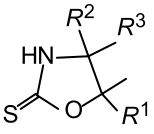


	R^1	R^2	R^3
61a:	*Me*	*Me*	*Me*
61b:	*Ph*	*Me*	*Me*









	R^1	R^2	R^3
63a:	CH_3	CH_3	CH_3
63b:	C_6H_5	CH_3	CH_3
63c:	C_6H_5	C_6H_5	C_6H_5

	R	R^1	R^2	R^3
62a:	CH_3	CH_3	CH_3	CH_3
62b:	CH_3	C_6H_5	CH_3	CH_3
62c:	CH_3	C_6H_5	C_6H_5	C_6H_5
62d:	C_2H_5	CH_3	CH_3	CH_3
62e:	C_2H_5	C_6H_5	CH_3	CH_3

Scheme 36

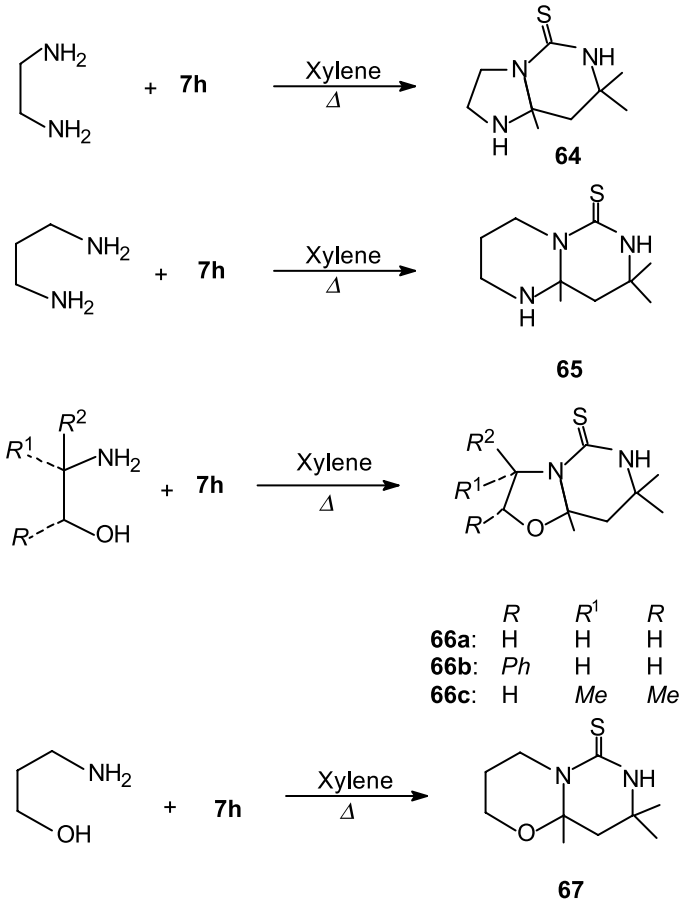
under basic and acidic conditions gave the pyrimidooxazine **67** and the *S*-methyl derivative of pyrimidooxazine **73** (Scheme 42).

Out of various compounds **64a**–**64b**, **72**, **67**, and **73** were screened for antiinflammatory activity [20]. Only **64a** showed weak antiinflammatory activity at 100 mg/kg *p.o.* *N*-Aminoadenosine (**74**) on condensation with **7h** gave **75** [43] (Scheme 43).

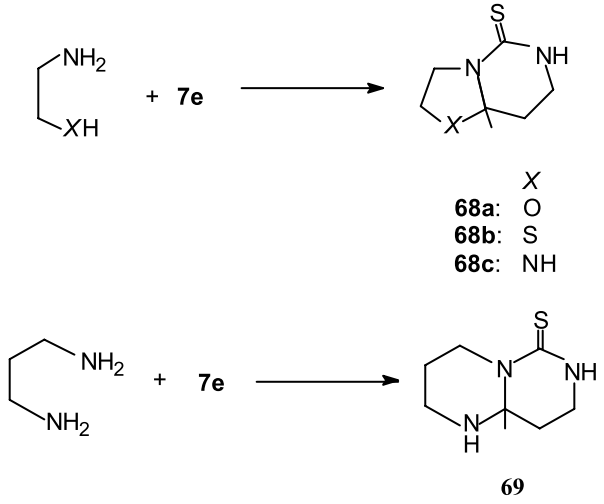
Glycine on condensation with **7h** gave oxazolopyrimidine **76** [40, 44], which undergoes rearrangement [44] upon boiling in hexanol to give **77**. However, glycine and anthranilic acid on condensation with **7e** gave products **78** and **79** [40] (Scheme 44).

Several bicyclic compounds were synthesized by the condensation of substituted hydrazines with β-isothiocyanatoketones to give **80**, which was cyclized by means of Me_3SiNCS to give bicyclic derivatives **81** [36] (Scheme 45).

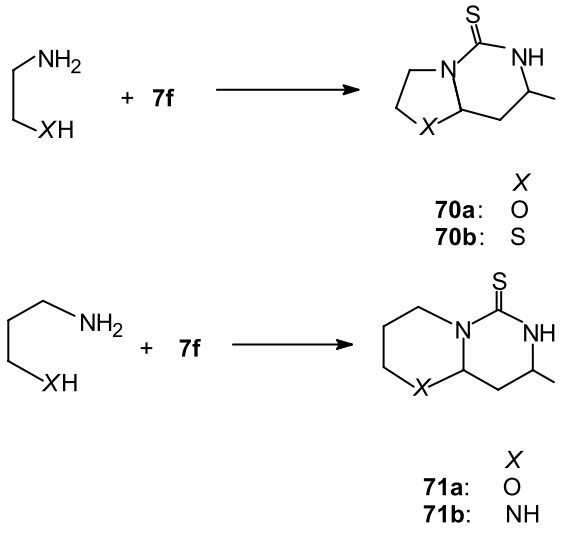
Singh et al. condensed cyclohex-1-enylaniline with **7h** to give 1,5-benzodiazocine-6(1*H*)-thione **82** as the major product and pyrimidine-2-thione **83** as the minor product [45] (Scheme 46).



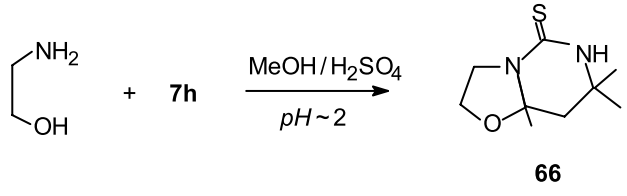
Scheme 37



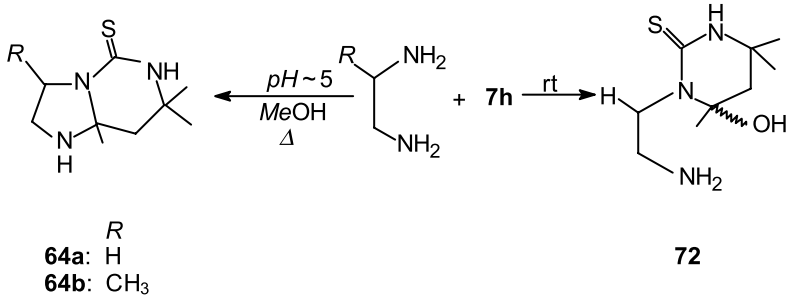
Scheme 38



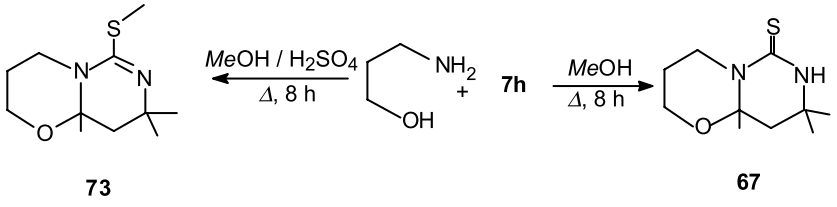
Scheme 39



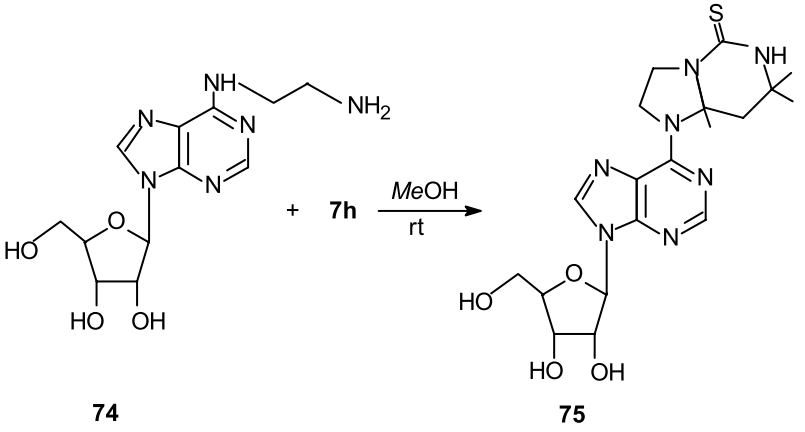
Scheme 40



Scheme 41

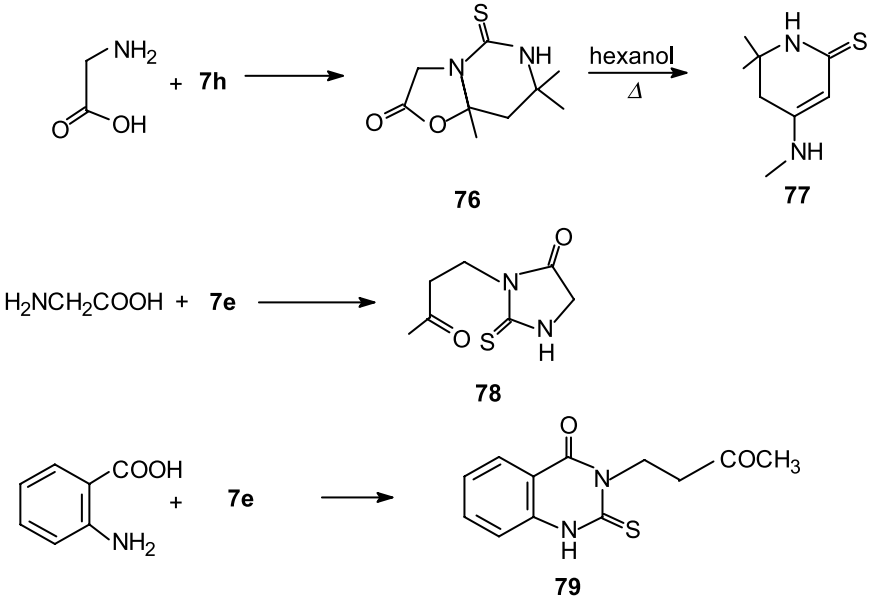


Scheme 42



74 75

Scheme 43



76 77

78

79

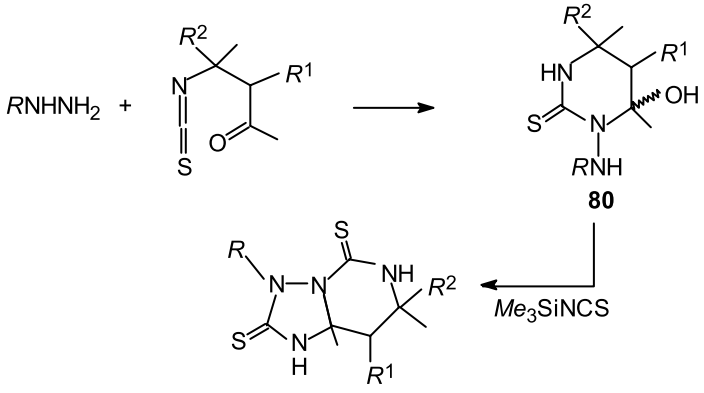
Scheme 44

The bicyclic fused ring system **85** was synthesized by condensation of hydrazine with **7h** to give the seven membered heterocycle **84** which was alkylated with $BrCH_2COOEt$ to give the bicyclic derivative **85** [35] (Scheme 47). 6*H*-Cyclopenta[*b*]-1,5-diazocine-6-thione **90** has been synthesized as shown in Scheme 48 [46].

The bicyclic compounds **91** and **92** were obtained by condensation of 3,4-dimethyl-1,2-phenylenediamine with **7a** [27] and 2,3-diaminopyridine with **7e** [26] (Scheme 49).

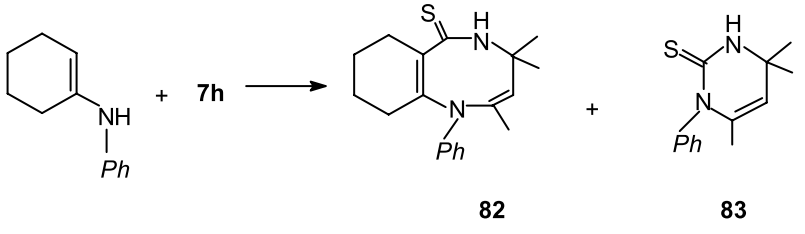
Synthesis of Tricyclic Derivatives

β-Isothiocyanatoketones have been used to synthesize a variety of tricyclic heterocyclic compounds [47]. Thus, 4,2′-anhydro-4-hydroxy-3-(3′,5′-*O*-isopropylidene-



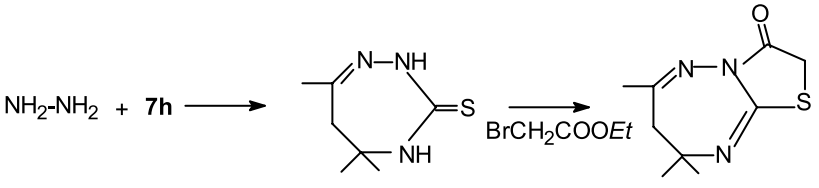
	R	R^1	R^2
81a:	C_2H_5	H	CH_3
81b:	$HOCH_2CH_2$	H	CH_3
81c:	$PhCH_2CH_2$	H	CH_3
81d:	C_6H_{11}	H	CH_3
81e:	*Ph*	H	CH_3
81f:	CH_3	H	CH_3
81g:	H	H	CH_3
81h:	*Ph*	CH_3	H

Scheme 45



82 **83**

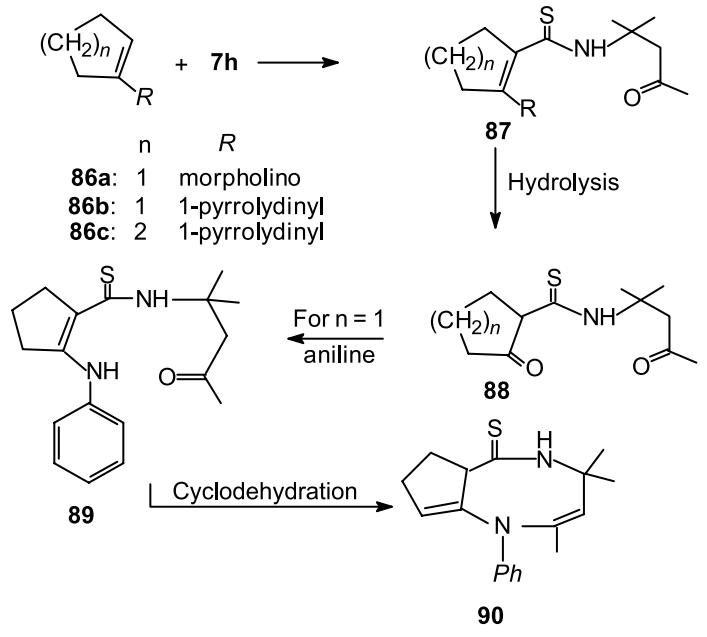
Scheme 46



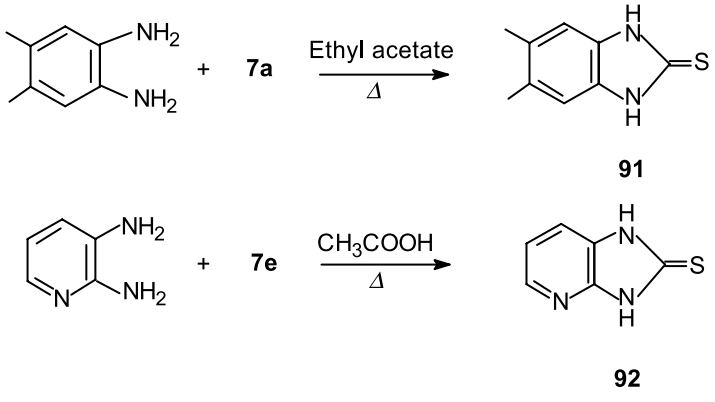
84 **85**

Scheme 47

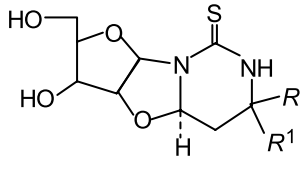
α-*D*-xylofuranosyl)hexahydro-2-pyrimidinethiones **93a** ($R = H$, $R^1 = H$), **93b** ($R = H$, $R^1 = Me$), and **93c** ($R = Me$, $R^1 = Me$) were prepared by reaction of 3,5-*O*-isopropylidenexylofuranosylamine tosylate with β-isothiocyanatoaldehydes in the presence of Et_3N (Scheme 50).



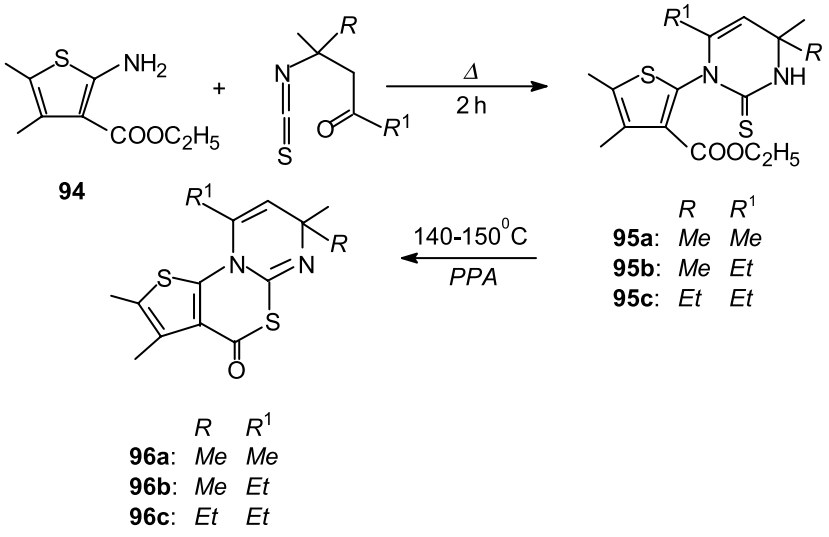
Scheme 48



Scheme 49



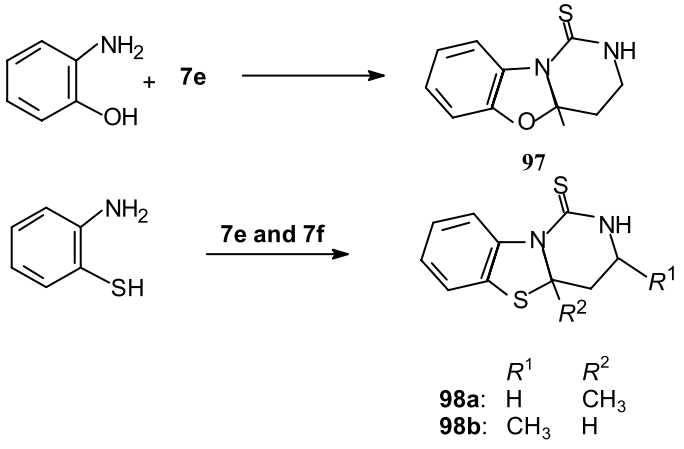
Scheme 50



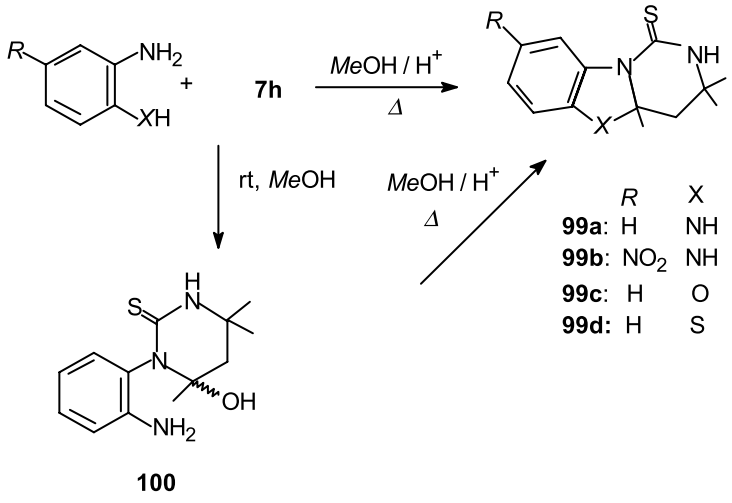
Scheme 51

Gakhar et al. synthesized pyrimido[2,1-*b*]thieno[2,3-*d*][1,3]thiazines **96** by condensation of 2-amino-3-carbethoxy-4,5-dimethyl thiophene (**94**) with β-isothiocyanatoketones [48] (Scheme 51).

Condensation of *o*-aminophenol and *o*-aminothiophenol with **7e** and **7f** under basic conditions gave pyrimidobenzoxazole and pyrimidobenzthiazole derivatives **97** and **98** [42] (Scheme 52). Condensation of **7h** with *o*-phenylenediamine, 4-nitro-*o*-phenylenediamine, *o*-aminophenol, and *o*-aminothiophenol under acidic conditions yielded pyrimidobenzimidazole **99a** and **99b**, pyrimidobenzoxazole **99c**, and pyrimidobenzthiazole **99d** derivatives [24] (Scheme 53). However, condensation of *o*-aminophenylenediamine with **7h** at room temperature gave hydroxy pyrimidine **100**, which was cyclized by heating under acidic conditions to give **99a**.



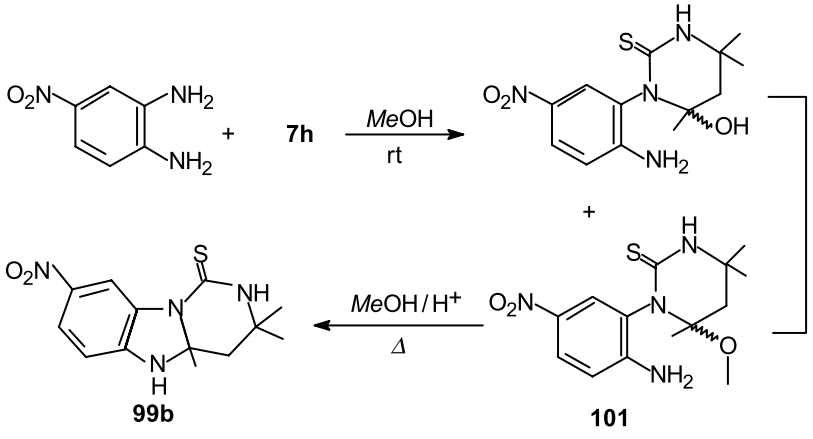
Scheme 52



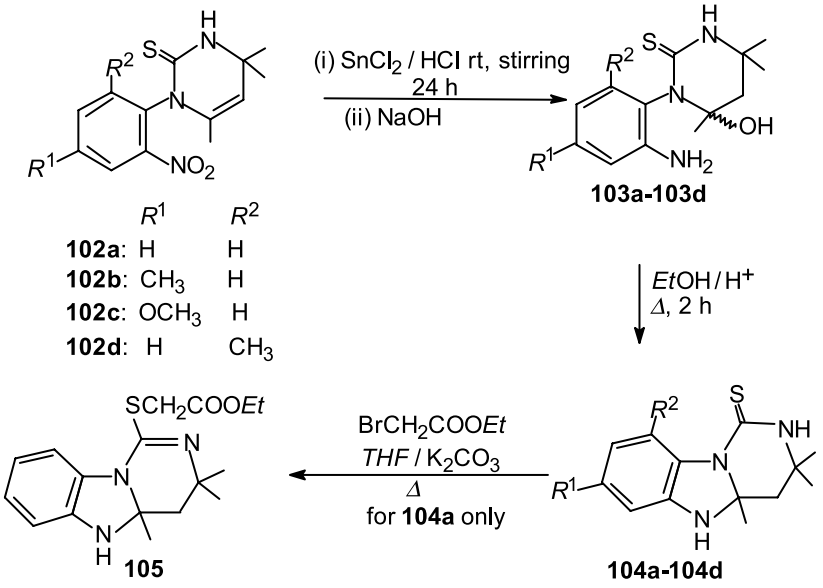
Scheme 53

Formation of **99b** is based on the fact that the more basic amino group, *i.e.* meta to the nitro group, will react first with isothiocyanatoketone and then the amino group para to nitro will undergo cyclization to give **99b**. Compounds **99b** and **99d** exhibited low antiinflammatory activity [20] at 100 mg/kg *p.o*. Condensation of 4-nitro-1,2-phenylenediamine with **7h** at room temperature gave a mixture of hydroxy and methoxy pyrimidines **101** which could be cyclized to **99b** by heating under acidic conditions [31] (Scheme 54). Reduction of nitropyrimidine derivatives **102** with $SnCl_2$/HCl yielded aminohydroxypyrimidines **103**, which on heating in ethanol under acidic conditions yielded tricyclic compounds **104**. Tricyclic compound **104a** on reaction with $BrCH_2COOEt$ gave the *S*-alkylated product **105** [49] (Scheme 55).

Compounds **104a**–**104c** were also prepared by direct condensation of *o*-phenylenediamines with **7h** under acidic conditions [50]. The reaction kinetics of



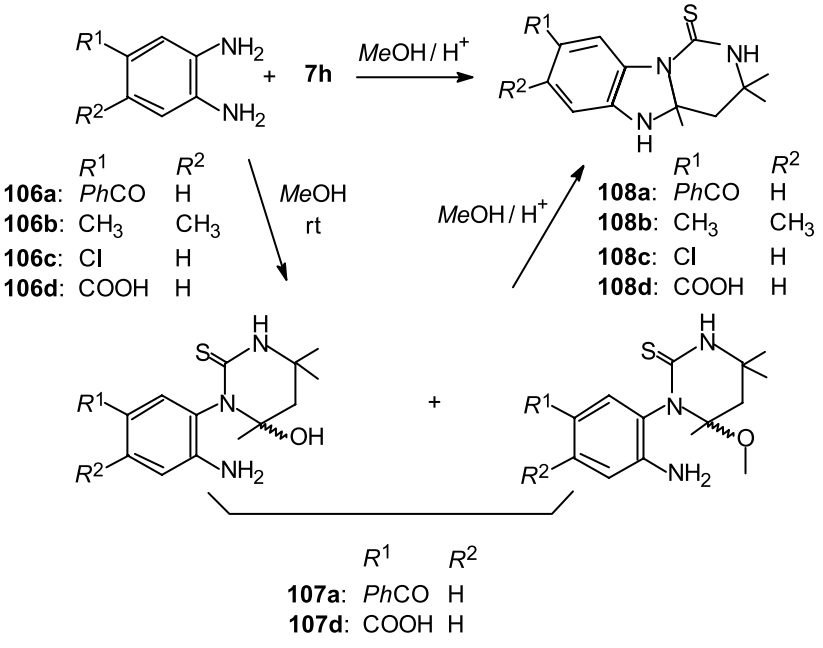
Scheme 54



	R^1	R^2
102a	H	H
102b	CH_3	H
102c	OCH_3	H
102d	H	CH_3

Scheme 55

cyclization of **103a**–**103c** to **104a**–**104c** have also been studied and the rate of cyclization was **103b** > **103a** > **103c**. Antiinflammatory activity evaluation [20] of **104a**–**104d** and **105** indicated that **104b** and **104c** possess 14 and 34% antiinflammatory activity at 100 mg/kg *p.o.* whereas **104c** exhibited 28% activity at 25 mg/kg *p.o.*, which is equipotent to phenylbutazone (30 mg/kg *p.o.*) [49].



	R^1	R^2
106a	*Ph*CO	H
106b	CH_3	CH_3
106c	Cl	H
106d	COOH	H

	R^1	R^2
108a	*Ph*CO	H
108b	CH_3	CH_3
108c	Cl	H
108d	COOH	H

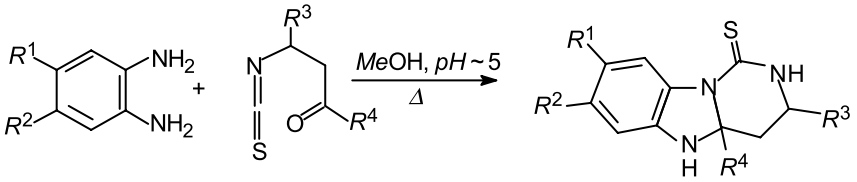
	R^1	R^2
107a	*Ph*CO	H
107d	COOH	H

Scheme 56

Condensation of substituted *o*-phenylenediamines **106a**–**106d** with **7h** gave the tricyclic products **108a**–**108d** as shown in Scheme 56 [25, 30]. From the four compounds, *i.e.* **108a**–**108d**, compound **108d** showed weak antiinflammatory activity.

Out of many tricyclic compounds reported, *S*-alkylation and *N*-acetylation of a few compounds is also described in literature [25, 43]. Some of the products showed moderate antiinflammatory activity. Condensation of *o*-aminophenol and *o*-aminothiophenol with **7h** under basic conditions by refluxing in an inert solvent yielded the corresponding tricyclic ring systems [22]. 3-Isothiocyanato-2-butanal (**7f**) [27] and 4-isothiocyanato-2- butanone (**7e**) [26] on condensation with various (un)substituted *o*-phenylenediamines gave the tricyclic pyrimidobenzimidazoles **109** (Scheme 57).

Compounds **109c** and **109i** were *S*-methylated to give **110a** and **110b.** Compounds **109a**–**109m** and **110b** were evaluated for antiinflammatory activity at 100 mg/kg *p.o*. Compounds **109b** and **109i** showed good (43, 46%) **109c**, **109h**, **109j**, and **109l** showed moderate (24, 21, 22, and 28%), whereas all other compounds showed weak antiinflammatory activity [20]. Compounds **109a**–**109m**



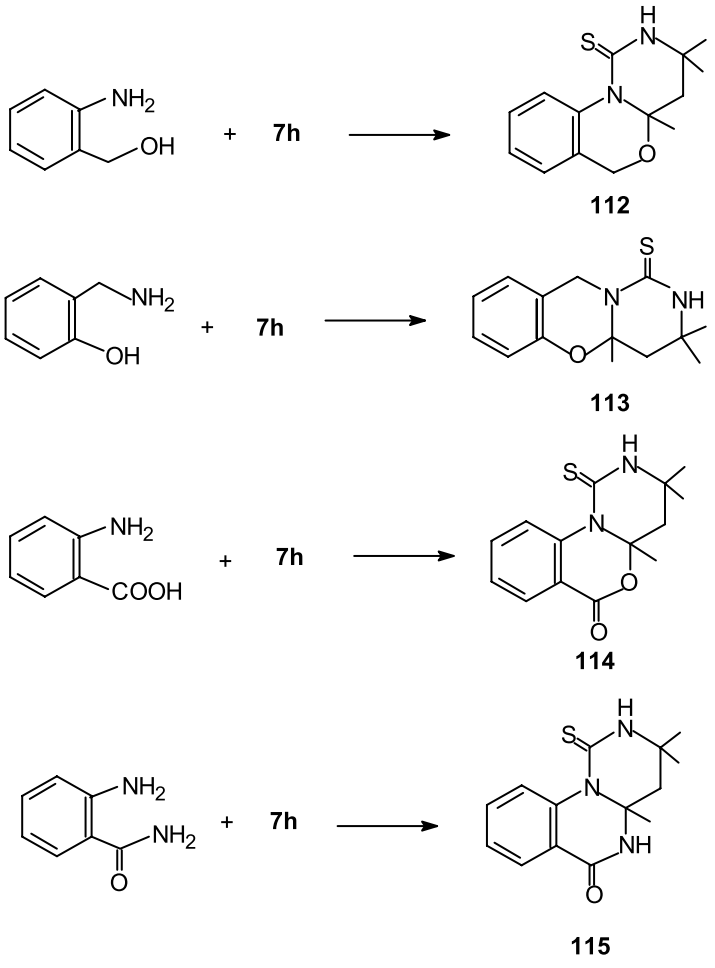
	R^1	R^2	R^3	R^4
109a:	H	H	H	CH_3
109b:	NO_2	H	H	CH_3
109c:	*Ph*CO	H	H	CH_3
109d:	H	CH_3	H	CH_3
109e:	CH_3	CH_3	H	CH_3
109f:	COOH	H	H	CH_3
109g:	H	H	CH_3	H
109h:	H	CH_3	CH_3	H
109i:	NO_2	H	CH_3	H
109j:	COOH	H	CH_3	H
109k:	H	Cl	CH_3	H
109l:	*Ph*CO	H	CH_3	H
109m:	CH_3	CH_3	CH_3	H

	R^1	R^2	R^3	R^4
110a:	*Ph*CO	H	CH_3	H
110b:	*Ph*CO	H	H	CH_3

Scheme 57

111

Scheme 58



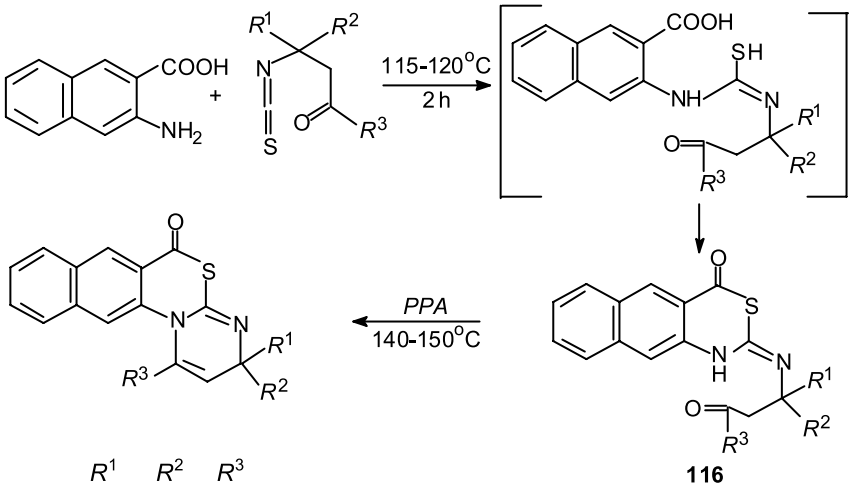
Scheme 59

showed good antiamoebic activity [51–53]. Condensation of 2,3-diaminopyridine with **7h** yielded pyrimidopyridoimidazole **111** [26] (Scheme 58), which showed good antiinflammatory (34% at 100 mg/kg *p.o.*) [20] and antiamoebic [51–53] activities.

Zigeuner et al. [22, 44, 54] and *Singh* et al. [40] condensed **7h** with *o*-aminobenzylalcohol, *o*-hydroxybenzylamine, anthranilic acid, and anthranilamide to give compounds **112**, **113**, **114**, and **115** (Scheme 59).

Synthesis of Tetra- and Pentacyclic Compounds

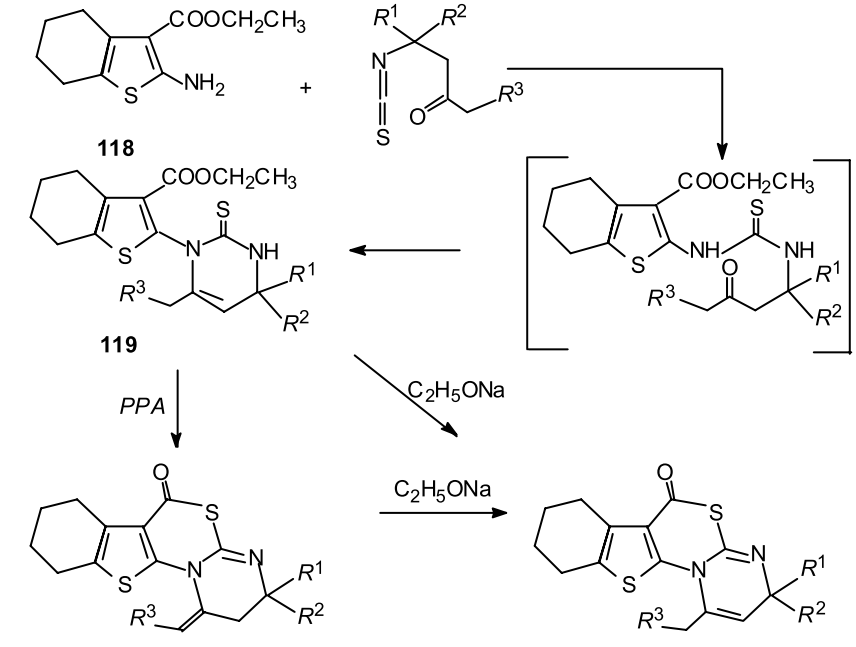
A number of tetra- and pentacyclic compounds have been synthesized using isothiocyanatoketones. Thus, *Gakhar* et al. [55] prepared naphtho[2,3-*d*]pyrimido[2,1-*b*][1,3]thiazine derivatives **117** by condensing 3-amino-2-naphthoic acid with β-isothiocyanatoketones and finally cyclizing the intermediate **116** with polyphosphoric acid (*PPA*) to yield **117** as shown in Scheme 60.



116

	R^1	R^2	R^3
117a:	CH_3	CH_3	CH_3
117b:	CH_3	CH_3	C_2H_5
117c:	CH_3	C_2H_5	C_2H_5

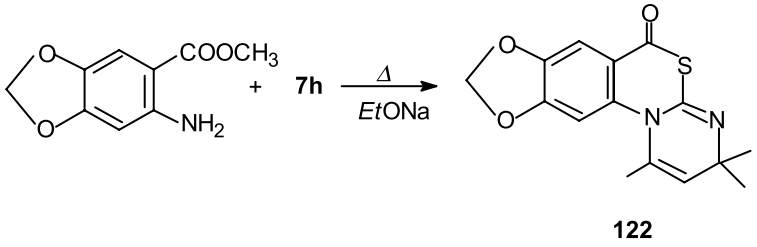
Scheme 60



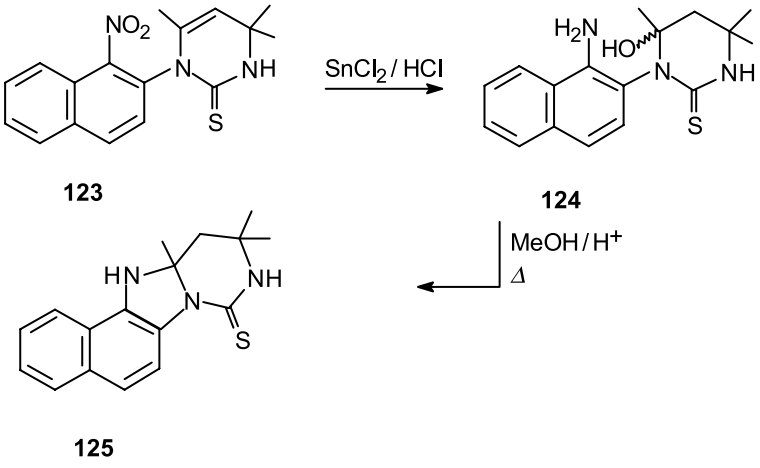
	R^1	R^2	R^3
120a:	CH_3	CH_3	H
120b:	CH_3	CH_3	CH_3
120c:	CH_3	CH_3	C_2H_5

	R^1	R^2	R^3
121a:	CH_3	CH_3	H

Scheme 61

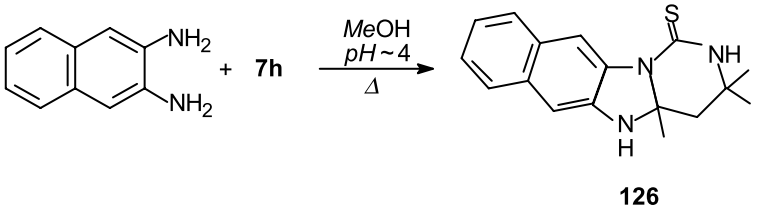


Scheme 62

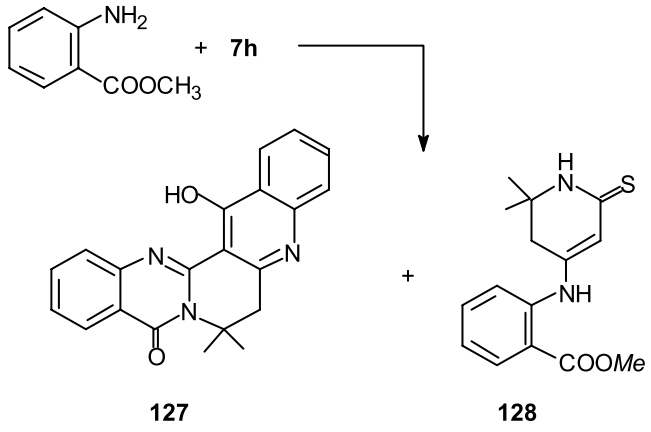


Scheme 63

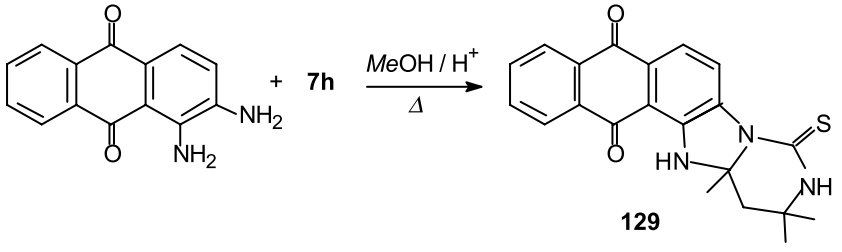
Condensation of **118** with β-isothiocyanatoketones gave an intermediate **119**, which on cyclization with *PPA* yielded **120**. Cyclization of **119** using sodium ethoxide gave **121** [56] (Scheme 61). The tetracyclic ring system **122** has been synthesized according to Scheme 62 [57]. *Sondhi* et al. [31] synthesized the tetracyclic derivative **125** by reduction of nitropyrimidine **123** (obtained from β-isothiocyanatoketone **7h** and 2-amino-1-nitro naphthalene) with $SnCl_2$/HCl to **124**. The later was cyclized under acidic condition to give the tetracyclic derivative (Scheme 63).



Scheme 64



Scheme 65



Scheme 66

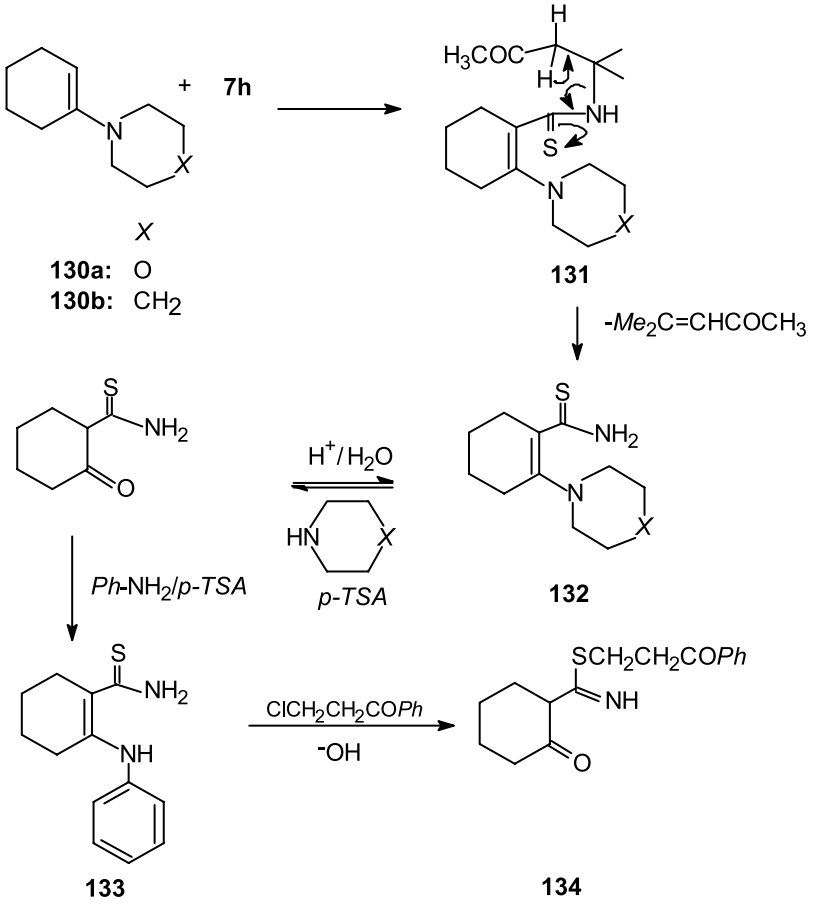
Condensation of 2,3-diaminonaphthalene with **7h** at $pH \sim 4$ gave 3,4,4a,5-tetrahydro-3,3,4a-trimethylpyrimido[1,6-*a*]naphthoimidazol-1(2*H*)thione (**126**) [43] (Scheme 64).

Zigeuner et al. [54, 58] synthesized the triazapentaphene **127** according to Scheme 65. Compound **128** arises from rearrangement of the initial normal condensation product. Condensation of 4-isothiocyanato-4-methyl-2-pentanone (**7h**) with 1,2-diaminoanthraquinone under acidic conditions yielded pyrimidoanthraquinonimidazole **129** [31] (Scheme 66), which exhibited moderate antiinflammatory activity (19%) at 100 mg/kg *p.o.* [20].

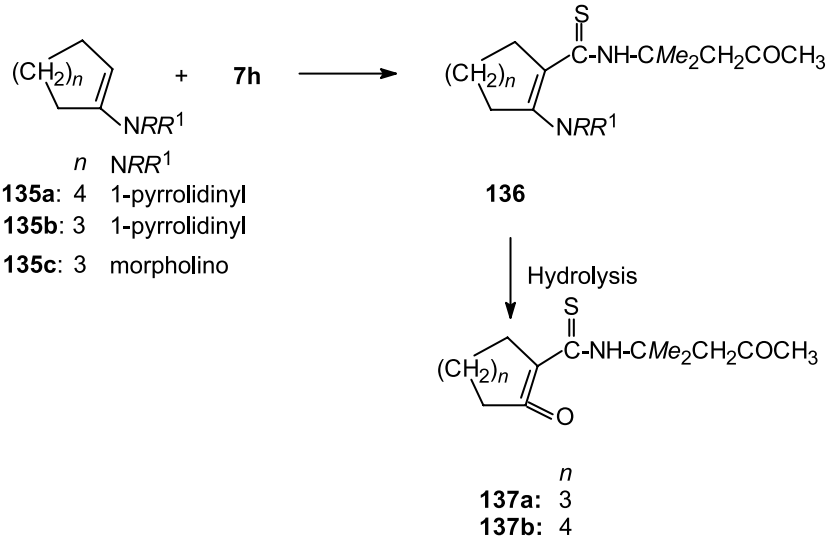
Miscellaneous Reactions

On condensation of **7h** with 1-piperidino and 1-morpholinocyclohexene **130a** and **130b** gave **131**, which underwent β-elimination to give 1-morpholino- and 1-piperidino-2-thioamidocyclohexenes **132** (Scheme 67) [59, 45].

Condensation of **7h** with compounds **135** gave the condensed products **136**, which on hydrolysis gave carbothioamides **137** [60] (Scheme 68).



Scheme 67



Scheme 68

Conclusion

β-Isothiocyanatoketones are useful reagents for the synthesis of heterocyclic compounds. Many compounds synthesized by using β-isothiocyanatoketones have shown good antiinflammatory activity and hence more compounds using β-isothiocyanatoketones should be prepared and screened for antiinflammatory activity. This may lead to the identification of more potent compounds.

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