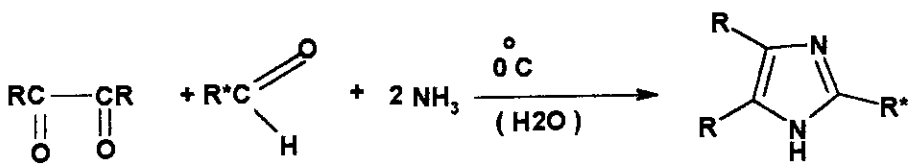
SYNTHESIS AND CHEMICAL REACTIONS OF IMIDAZOLE DERIVATIVES

A-SYNTHESIS OF IMIDAZOLE DERIVATIVES

1) From dicarbonyl derivatives

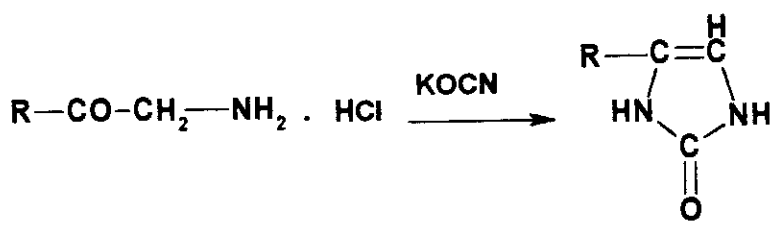
Imidazole ring can be synthesized by condensing alpha-dicarbonyl compounds, aldehydes and ammonia.[1]



(1) (2)

R,R*=H, alkyl, Ar

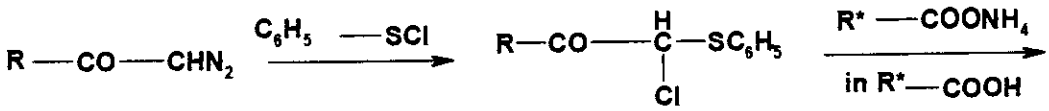
Also the reaction of α-amino ketones with potassium cyanate afforded 2-imidazolones in good yield.[2]



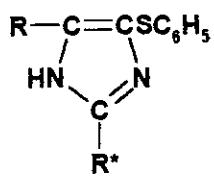
(3) (4)

Imidazoles could be also obtained by the action of liquid carboxylic acids which has been passed into NH_3, on α-chloro-α-

phenylmercaptoketones,[3] (obtained from diazoketones through reaction with C_6H_5SCl).



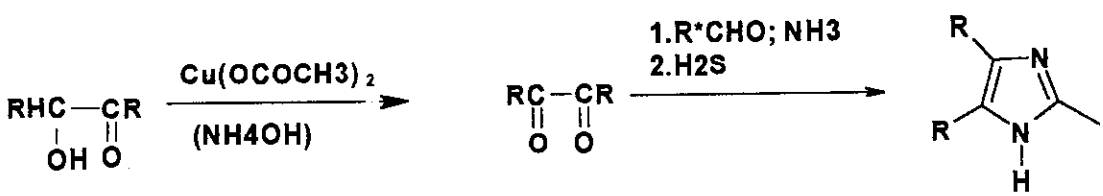
(5) (6)



(7)

2)Weidenhagen modification

Using acylonies gives better product gain.[4]

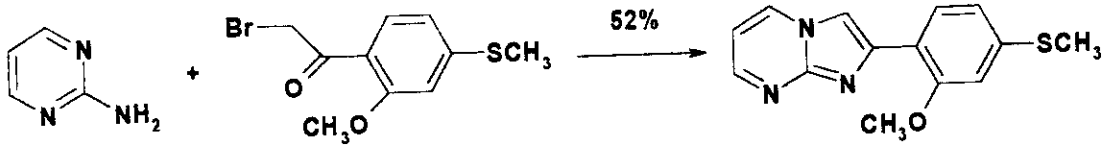


(8) (9) (10)

3-Synthesis of condensed imidazole derivatives

a-Imidazo[1,2-a]pyrimidine derivatives

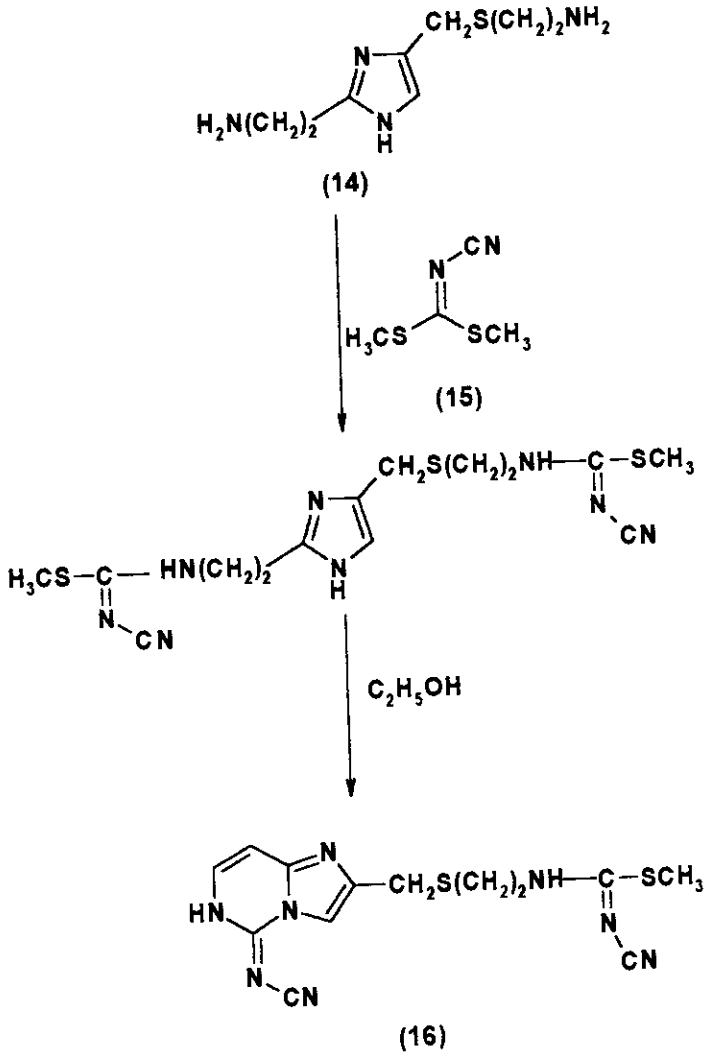
2-Aminopyrimidine **(11)** reacted with 1-[(4-methylthio)-2-methoxyphenyl]-3-bromoacetone **(12)** to produce 2-(*p*-methylthio)arylimidazo[1,2-a]pyrimidines **(13)**.[5]



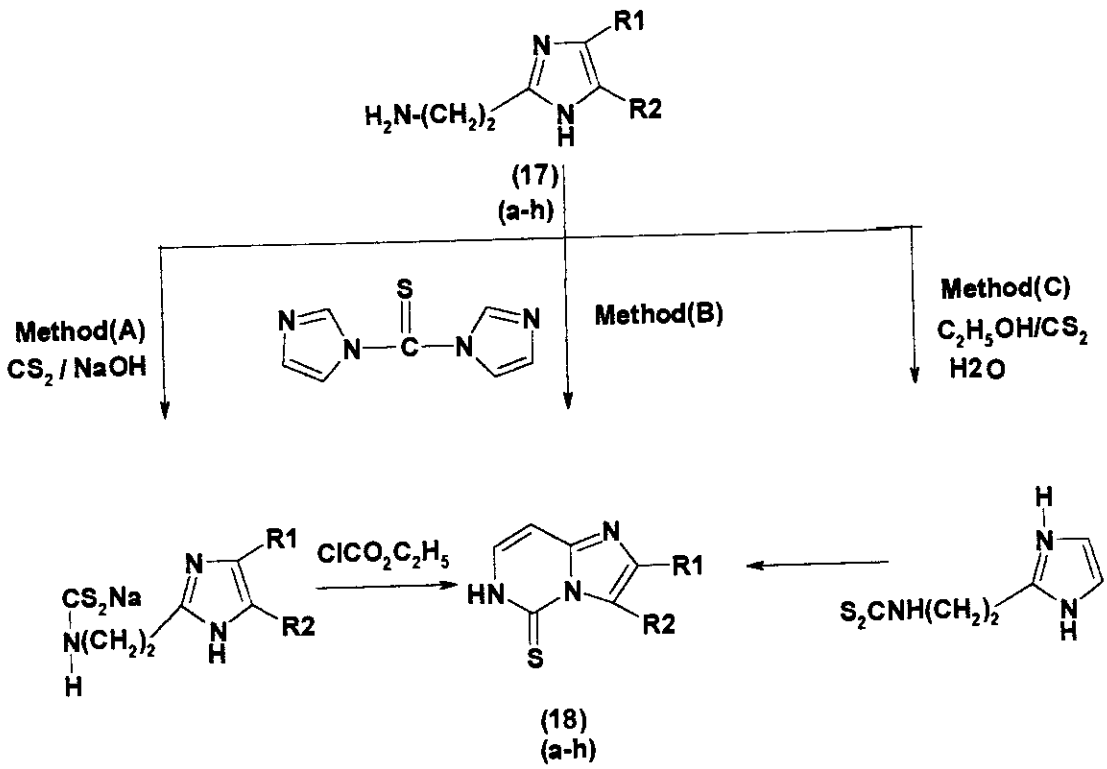
(11) (12) (13)

b-Imidazo[1,2-c]pyrimidine derivatives:

Condensation of isohistamine **(14)** with N-cyanodithioimidocarbonate **(15)** yielded (7,8-dihydroimidazo[1,2-c]pyrimidin-5(6H)-yieldine) cyanamid **(16)**.[6,7]



7,8-Dihydroimidazo[1,2-c]pyrimidine-5-thione derivatives **(18)** were synthesized from imidazole derivatives **(17)** by three different ways.[6,8]

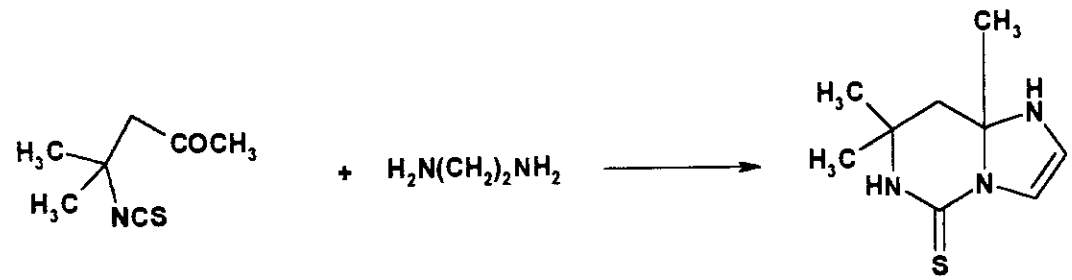


18	R1	R2
a	H	H
b	CH3	CH3
c	CH3	H
d	CH2OH	H

18	R1	R2
f	C_6H_5	H
g	$CH_2(CH_2)_2CH_2$	H
h	CH=CH CH=CH	H

C-Imidazo[1,5-a]pyrimidine derivatives

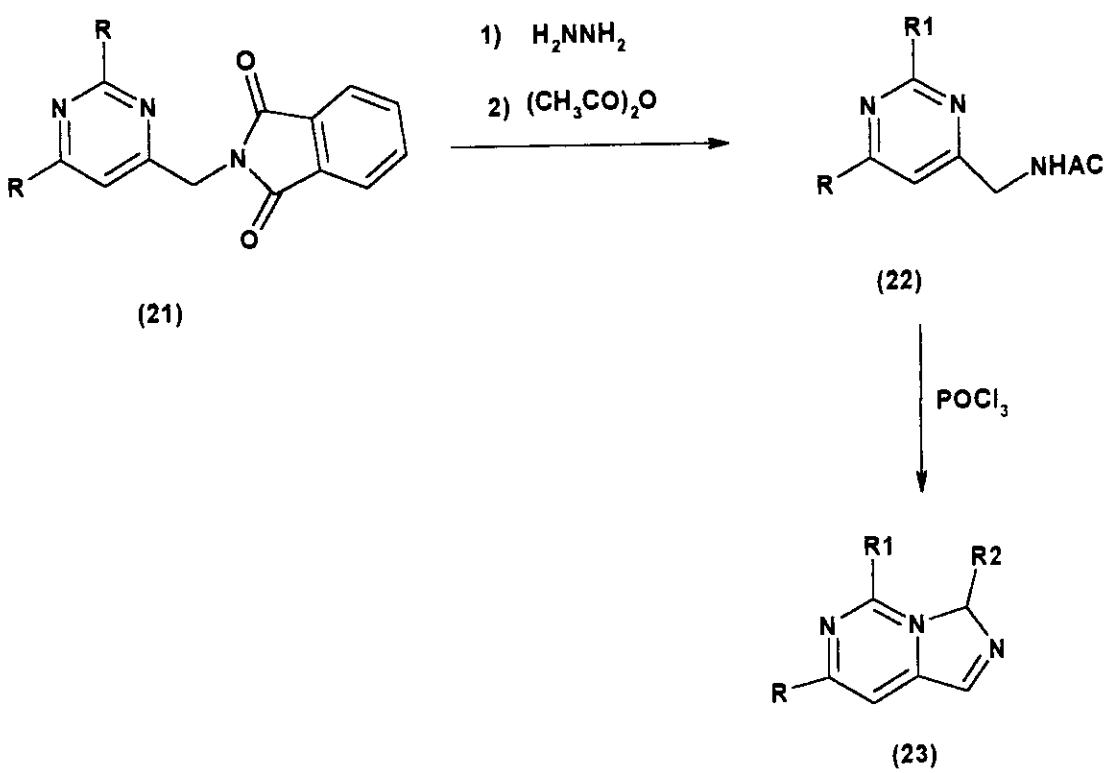
Condensation of ethylenediamine with 4-isothiocyanato-4-methyl-2-pentanone **(19)** yielded 2,6,7 tetrahydro 3,3-dimethyl imidazo[1,2-c]pyrimidine-5-thione **(20)**.[9]



(19) **(20)**

d-Imidazo[1,5-c] pyrimidine derivatives

2,4-Bis(methylthio)-6-(phthalimidomethyl)pyrimidine **(21)** reacted with hydrazine followed by acetylation gave compounds **(22)**, which were cyclized to give mercaptopurine derivatives **(23)**.[10]

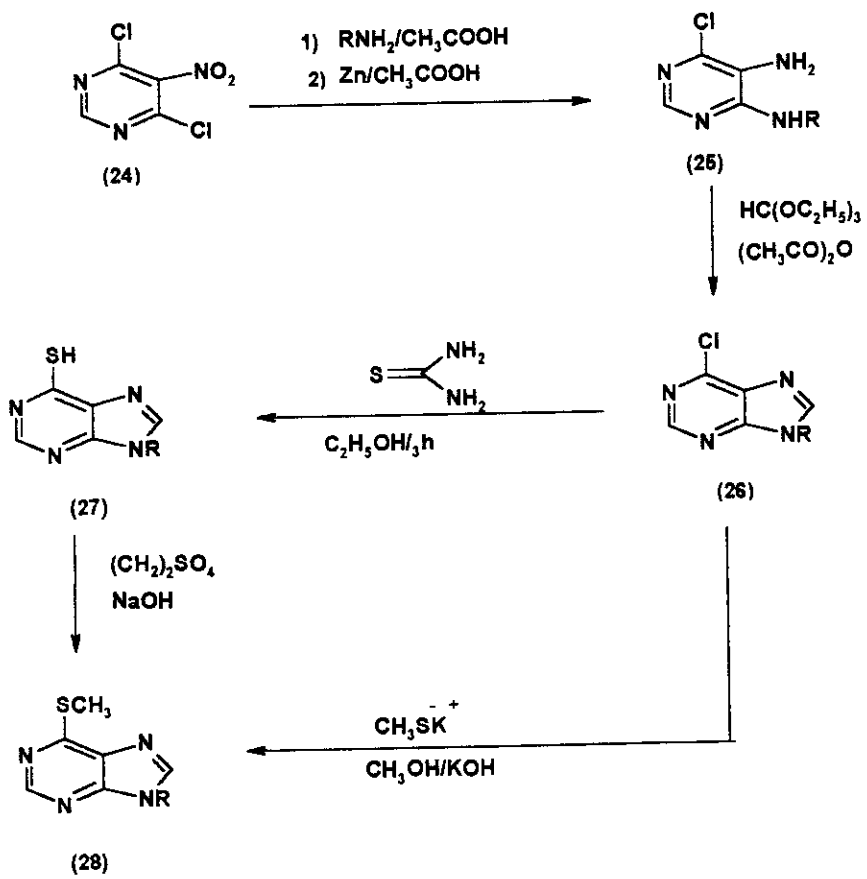


(21) **(22)** **(23)**

23	R	R1	R2
a	Alkythio	SH	H
b	Alkylthio	SC_6H_5	Alkyl
c	Morpholine	Alkylthio	C_6H_5

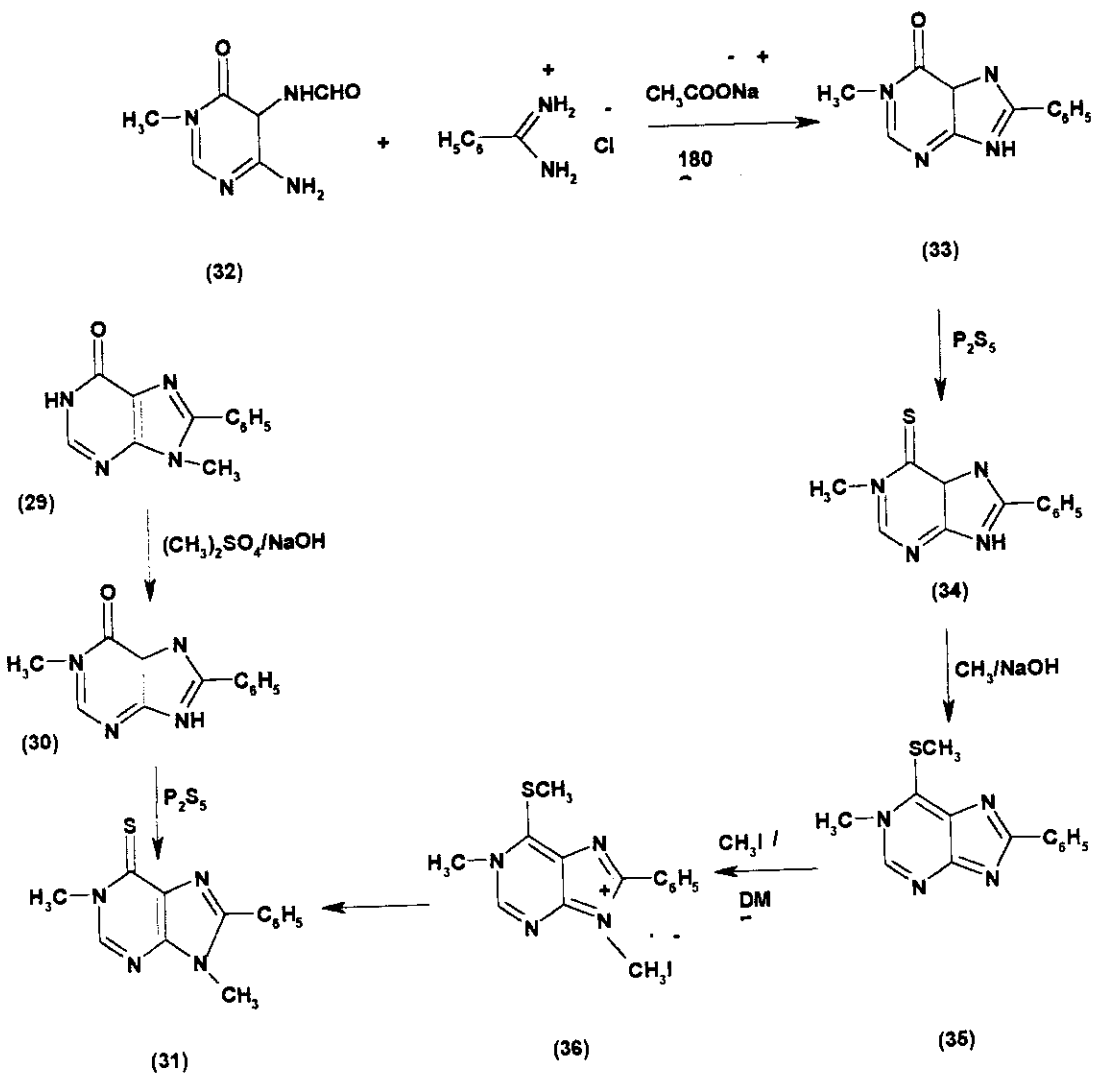
(1) 6-Methylthioimidazo[4,5-d]Pyrimidines

4,6 Dichloro-5-nitropyrimidine **(24)** was treated with alkyl amine derivatives to give compound **(25)** which were cyclized with ethyl orthoformate to 9-alkyl-6- substituted purines **(26).** Compounds **(26)** reacted with thiourea followed by methylation and reaction with methyl mercaptane to afford 9-alkyl-6-mercaptopurines **(28).**[11-20]

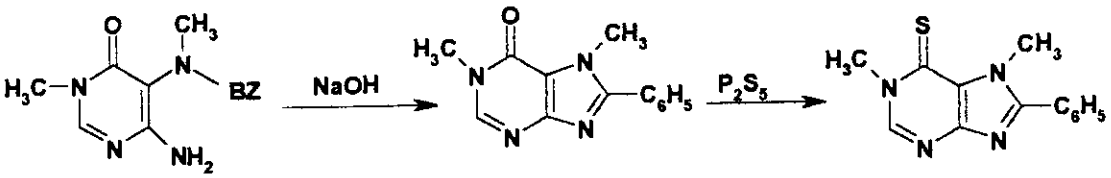


28	R	Yield %	m.p °C	Ref.
a	CH_3	50	171-172	13
b	C_2H_5	51	116-118	11

Methylation of 9-methyl-8-phenylhypoxyanthine **(29)** followed by thiation afforded the 6-thiopurine **(31)** that formed by another method, starting with 4-amino-5-formamido-1-methylpyrimidin-6-one **(32)**.[21-30]



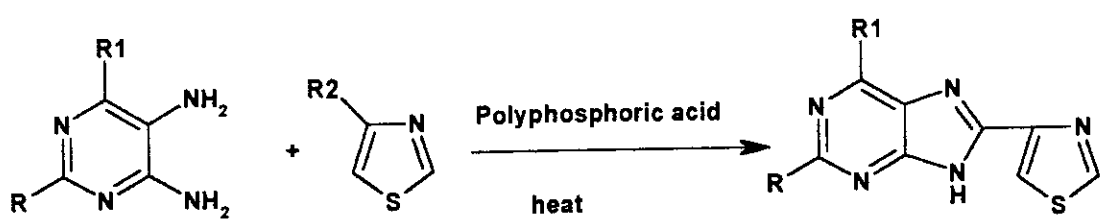
Cyclization of 4-amino-5-(N-methylbenzamido)pyrimidin-6-one (**37**) afforded 1,7-dimethyl-8-phenylimidazo[4,5-d]pyrimidin-6-one (**38**). Thiation of compound (**38**) yielded 6-thiopurines (**39**).[21]



(37) (38) (39)

BZ= COC_6H_5

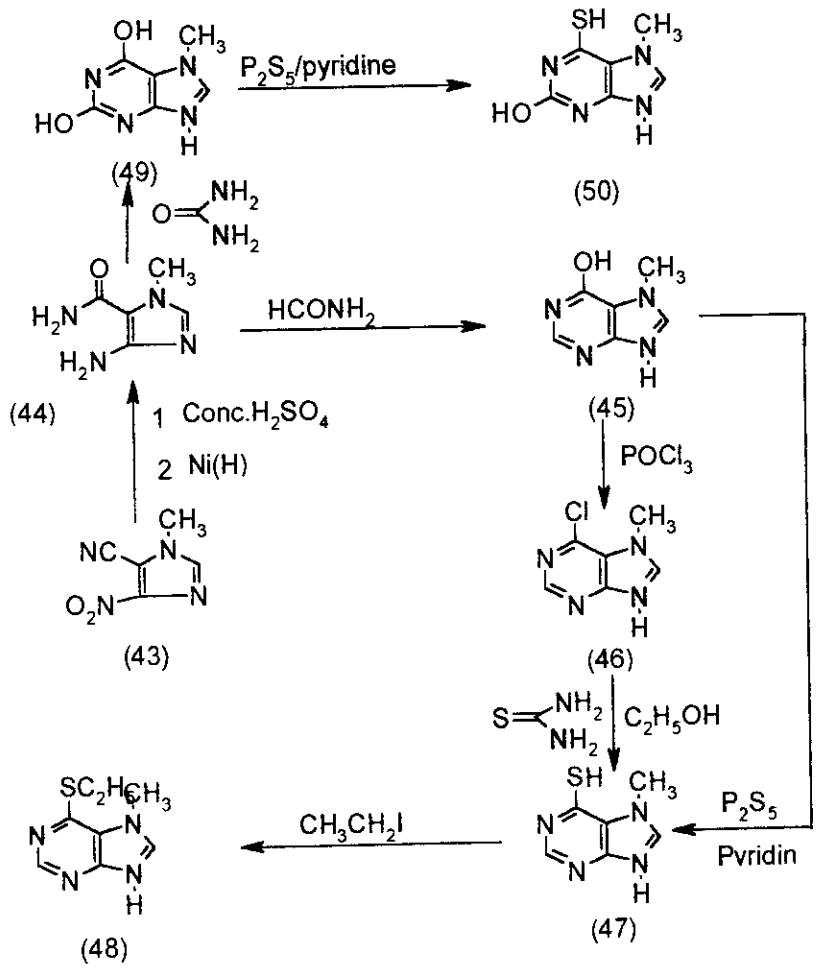
Condensation of 4-substitutedthiazole derivatives (**41**) with 4,5-diaminopyrimidines (**40**) afforded 8-(4-thiazolyl) mercaptopurines (**42**).[31-38]



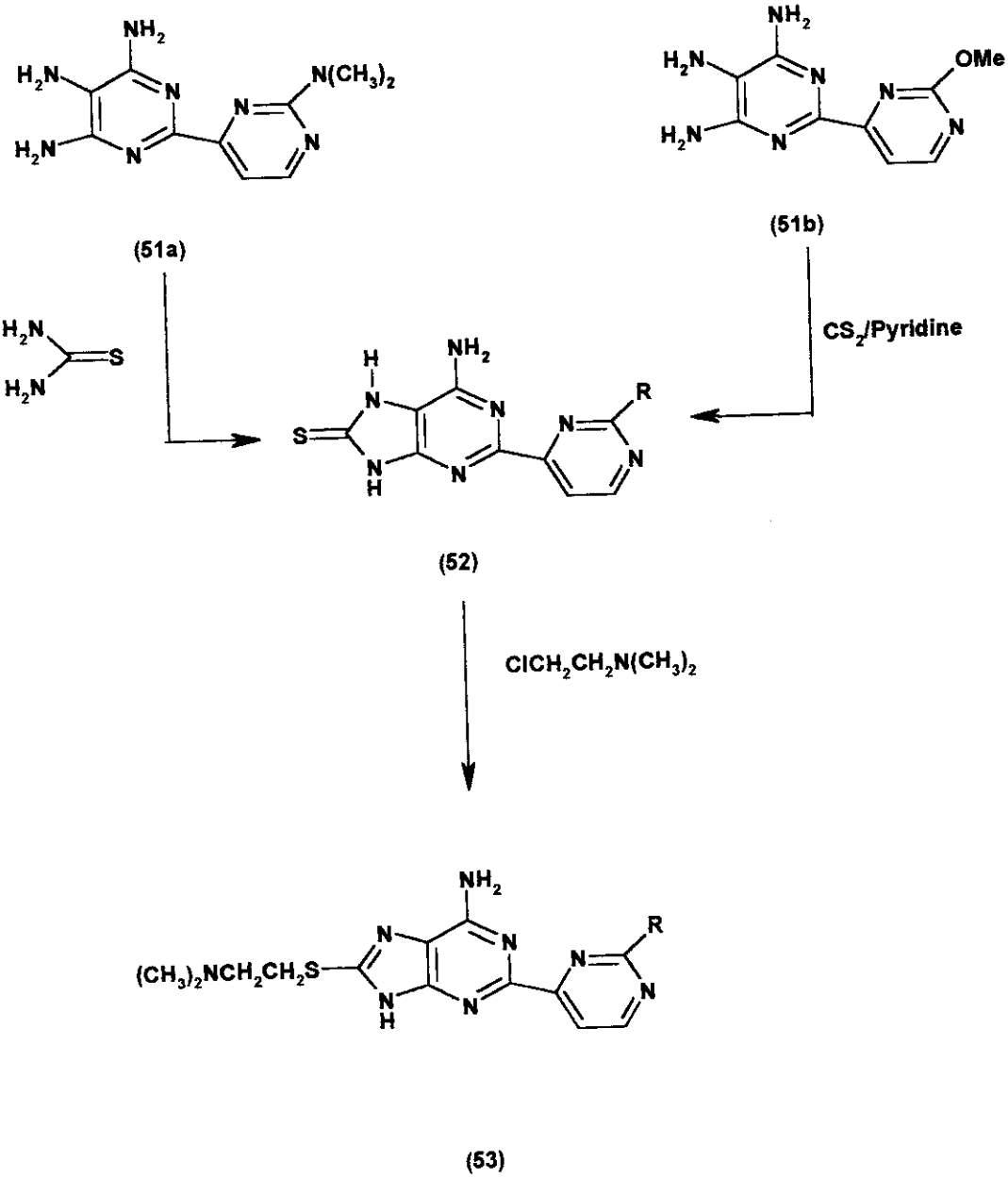
(40) (41) (42)

42	R	R1	R2
a	H	SH	CN
b	H	SCH_3	$CONH_2$
c	NH_2	SH	$CONH_2$

Hydrolysis and reaction of 1-methyl-4-nitro-5-imidazolecarbonitrile **(43)** gave 4-amino-1-methyl-5-imidazolecarboxamide **(44)**. The latter when reacted with formamide followed by reaction with phosphorous oxychloride yields 6-chloro-7-methylpurine **(46)**. Treatment of compound **(46)** with thiourea followed by ethylation afforded 6-ethylthio-7-methylpurine **(47)**. Fusion of compound **(44)** with urea followed by thiation gave 6-mercapto-7-methylpurine **(50)**.[39-51]

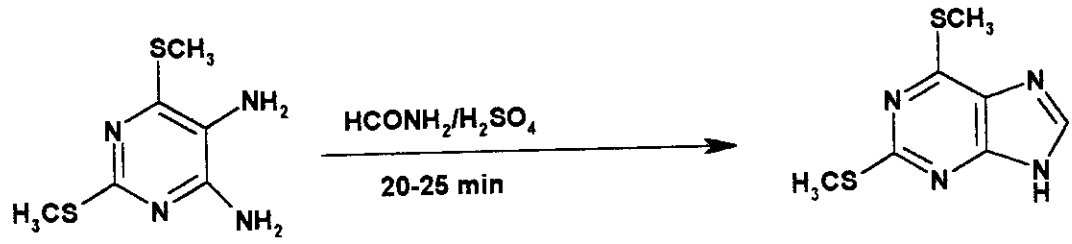


Fusion of 2-dimethylamino-2,4-bipyrimidin-4,5,6-triamine **(51)** with thiourea gave 6-amino-2-(2`-dimethylaminopyrimidin-4-yl)purin-8(7H)-thiones **(52)**. On the other hand, the triamine **(51b)** was converted into the thiones **(52)** by boiling with carbon disulfide in pyridine and subsequent.*S*-alkylation gave 8-(2-dimethylaminoethyl)thio-2-(2`-methoxypyrimidin-4`-yl)purin-6-amines **(53)**.[52-53]



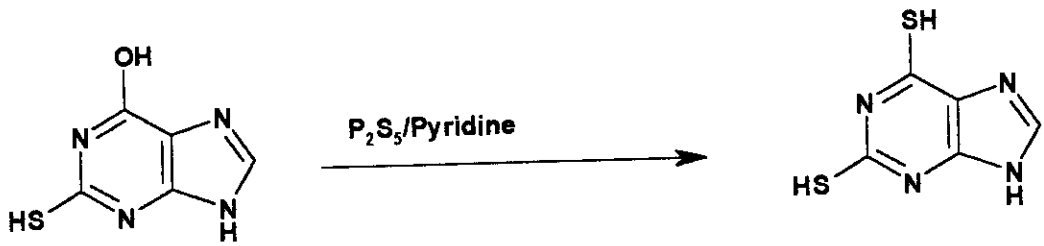
53	R	Yield %	m.p °C
a	$N(CH_3)_2$	61	236
b	OCH_3	54	213

Formylation of 4,5-dimethylthiopyrimidine **(54)** afforded the 2,6-dimethylmercaptopurine **(55)**.[54-56]



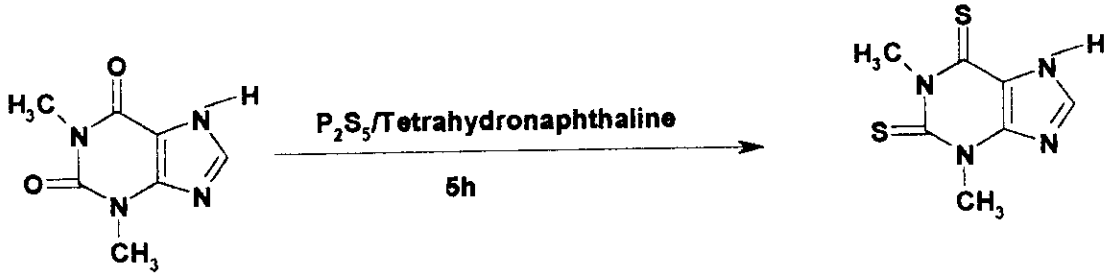
(54) **(55)**

On the other hand, 6-hydroxy-2-mercaptopurine **(56)** reacted with phosphorous pentasulfide to afford the corresponding 2,6-dimercaptopurine **(57)**.[57]



(56) **(57)**

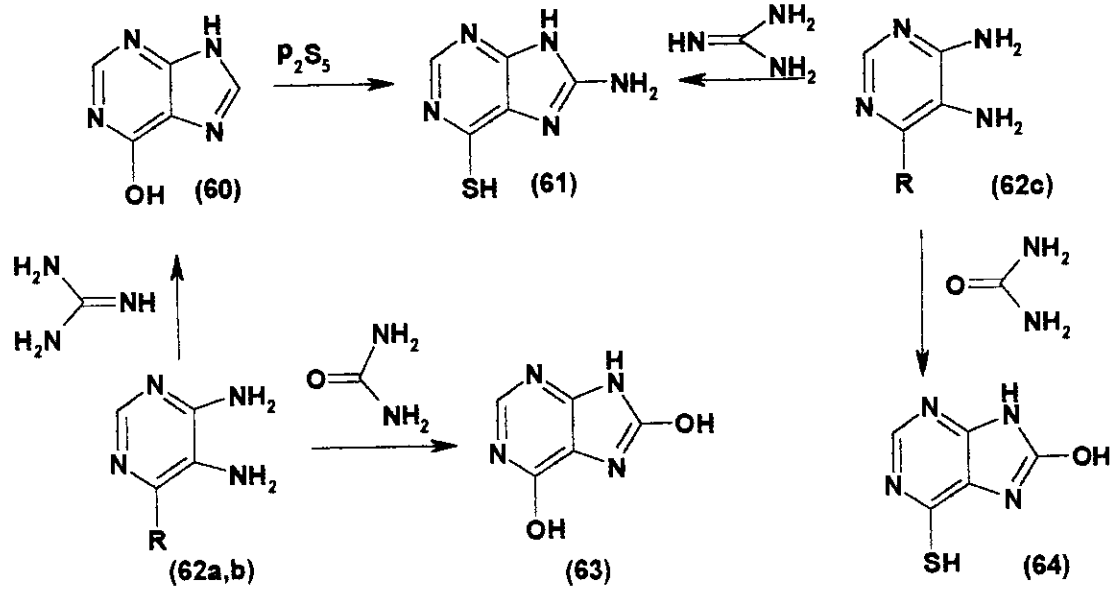
Similarly, 1,3-dimethyl-2,6-dithioxanthine **(59)** were prepared by thiation of theo phylline **(58)**.[58]



(58) (59)

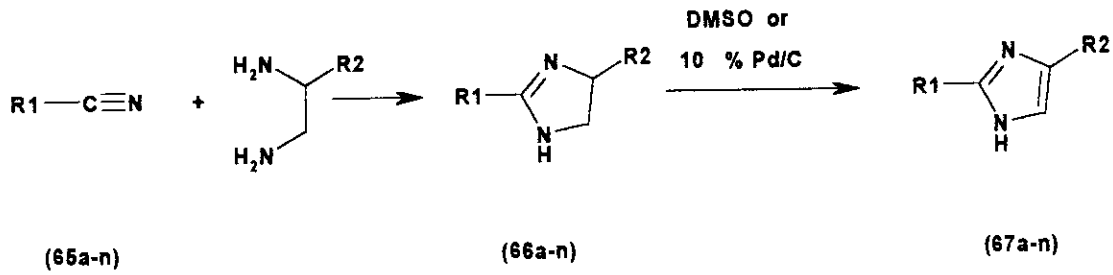
(2) 4,8-Dimethylthioimidazo[4,5-d]pyrimidines

Starting with 4,5-diamino-6-substituted pyrimidines (**62a-c**), 4-mercapto-, 8-methylmercapto-, and 4,8-dimethylmercaptopurines were prepared by multistep synthesizes.[59-65]



4)New one step synthesis of 2-Aryl-1H-Imidazoles

According to Swern oxidation,[66,67] 1*H*-imidazoles are readily available from reaction of nitrile compounds and diamines in the presence of oxalyl chloride, DMSO and triethylamine.



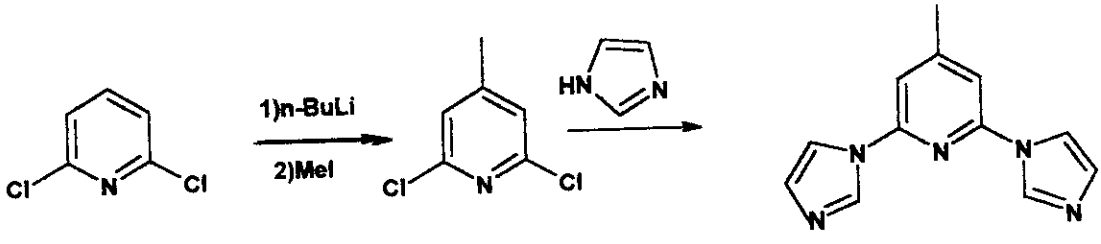
(65a-n) (66a-n) (67a-n)

R_1= Ph, *o*-,*m*-,*p*-tolyl, *o*-,*m*-,*p*-PhCl, *o*-,*m*-,*p*-$PhCF_3$, $PhCH_2$, 2-naphthyl, 2-benzofuranyl; R_2=H or CH_3

B-Reactions Of Imidazole Derivatives

1-Synthesis Of Heterocyclic 2,6-Bis(imidazol-1-yl)-4-methylpyridine

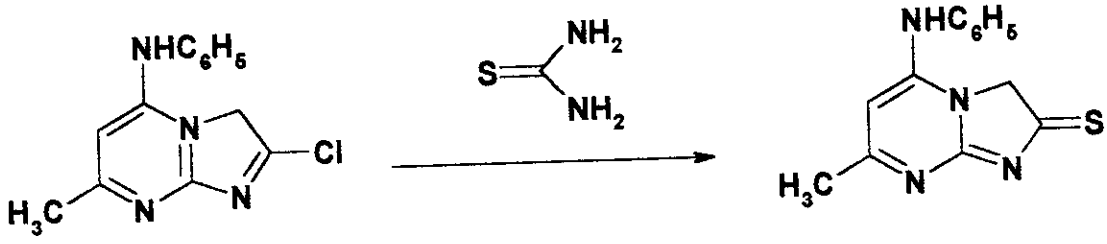
2,6-Bis(imidazol-1-yl)-4-methylpyridine **(68)** was prepared by reaction of imidazole, 2,6-dichloro-4-methylpyridine and potassium hydroxide using solid liquid PTC (without solvent) nucleophilic substitution conditions. The starting material, 2,6-dichloro-4-methylpyridine, was prepared by alkylation (*n*-BuLi/MeI) of 2,6-dichloropyridine according to a literature procedure.[68]



(68)

2)Reaction of imidazole derivatives with thiourea

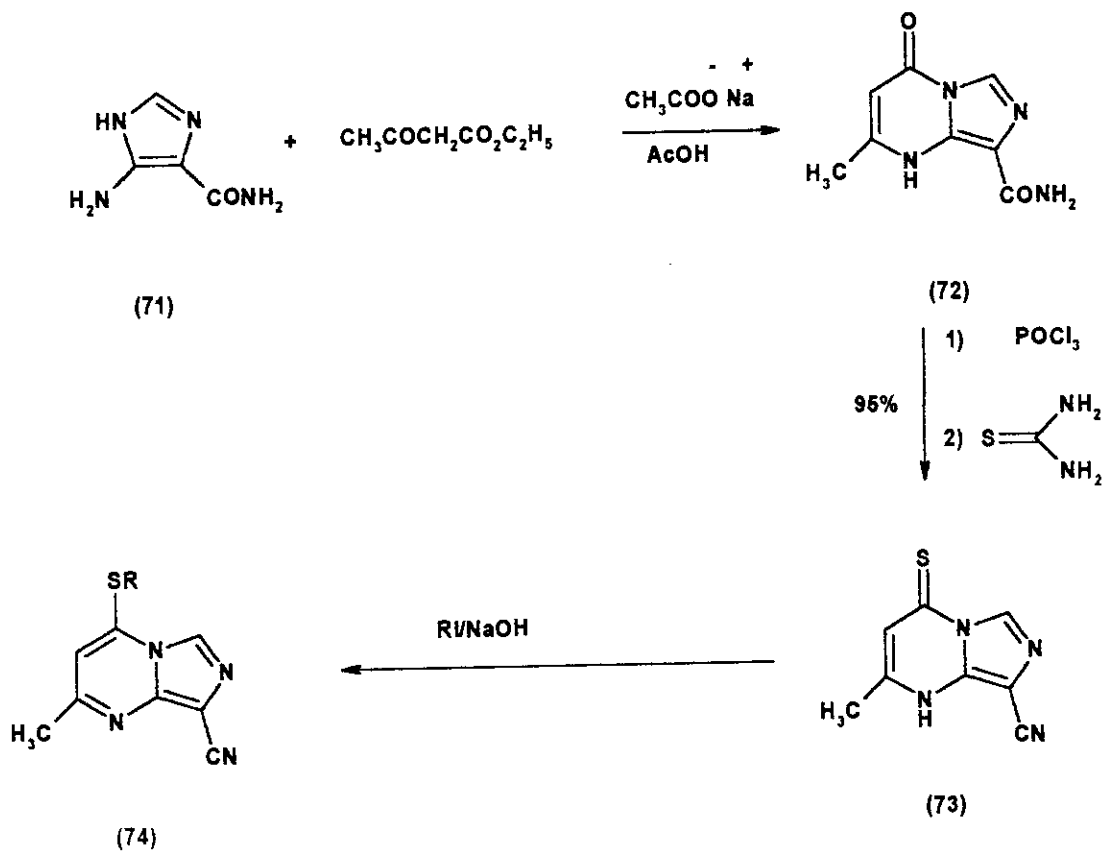
Treatment of 2-chloro-7-methyl-5-phenylaminoimidazo[1,2-a] pyrimidine **(69)** with thiourea yielded 7-methyl-5-phenylaminoimidazo[1,2-a]pyrimidin-2-thione **(70)**.[69-71]



(69) **(70)**

3)Reaction with active methylene compounds

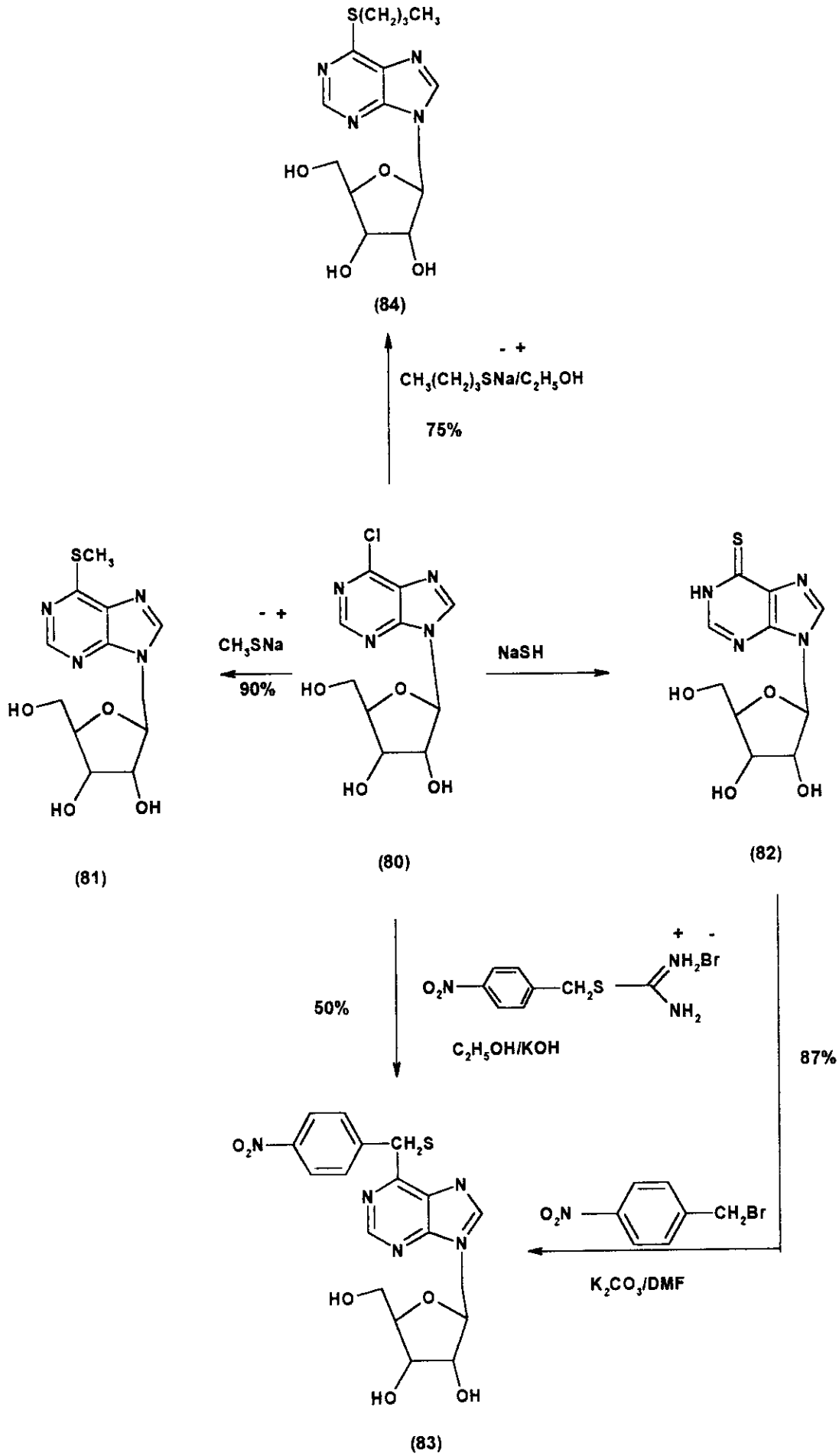
Similarly, condensation of 5(4)-aminoimidazole-4(5)-carboxamide (**71**) with ethyl acetoacetate yielded 3-methylimidazo [1,5-a]pyrimidin-(1H)-4-one-8-carboxamide (**72**). Dehydration and chlorination of compound (**72**) followed by reaction with thiourea afforded 8-cyano-2-methylimidazo [1,5-a] pyrimidin-(1H)-4-thione (**73**), which can be methylated to produce 8-cyano-2-methy-4-alkylthioimidazo[1,5-a] pyrimidines (**73**).[72-74]



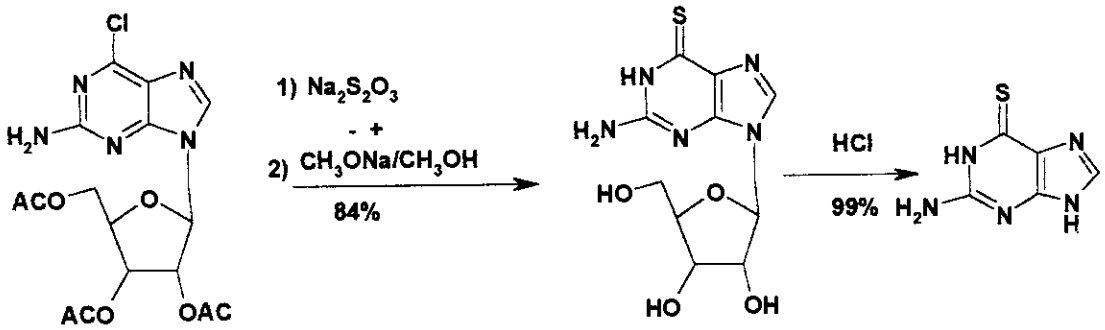
74	R	Yield %	Mp . °C
a	CH_3	43	210-212
b	C_2H_5	43	168-169
c	C_3H_7	52	139-141

b)Purine derivatives

Reaction of 6-chloro-9-deoxyribozidepurine **(80)** with methyl mercaptide and sodium mercaptide followed by reaction with *P*-nitrobenzyl bromide afforded 6-methylthio-9-(2-deoxy-β-D-erythropentofuranozyl)purine **(81)** and 6-*S*-(*P*-nitrobenzylthio)-9-(2-deoxy-β-D-erythropentofuranozyl)purine 33 respectively.On the other hand, compounds **(80)** reacted with benzyl mercaptide derivatives and n-butyl mercaptide to yield the corresponding compounds **(83)** and 6-(n-butylthio)-9-β-D-ribofuranosyl)purine **(84)** respectively.[83-98]

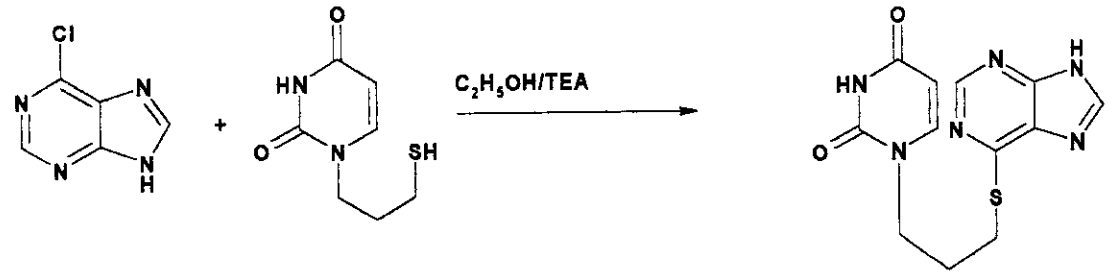

S(CH2)3CH3
(84)
- +
CH3(CH2)3SNa/C2H5OH
75%
SCH3
(81)
- +
CH3SNa
90%
Cl
(80)
NaSH
S
HN
(82)
87%
50%
+ -
NH2Br
O2N
CH2S
NH2
C2H5OH/KOH
O2N
CH2S
O2N
CH2Br
K2CO3/DMF
(83)

Treatment of 6-chloroguanosine 2,3,5-triacetate **(85)** with sodium thiosulfate gave 6-thioguanosine **(86)**. Hydrolysis of compound **(86)** afforded 6-thioguanine **(87)**.[99-102]



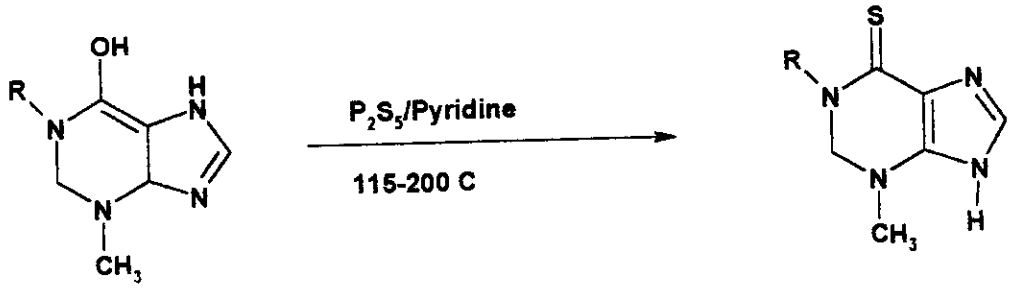
(85) (86) (87)

Reaction of 6-chloropurine **(88)** with thiol **(89)** in refluxing ethanol in presence of triethyl amine yielded the 6-[(n-propylpyrimidin-2,4-dione)thio]Imidazo[4,5-d]pyrimidine **(90)**.[103-104]



(88) (89) (90)

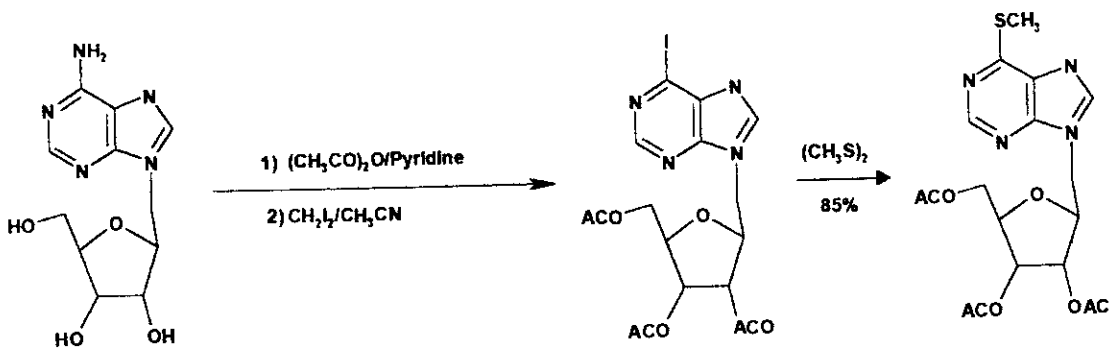
Purine-6-thione derivatives **(92)** were prepared by thiation of 6-hydroxy-3-methylpurine **(91)**.[58,105]



(91) (92)

92	R	Ref
a	H	61
b	CH_3	110

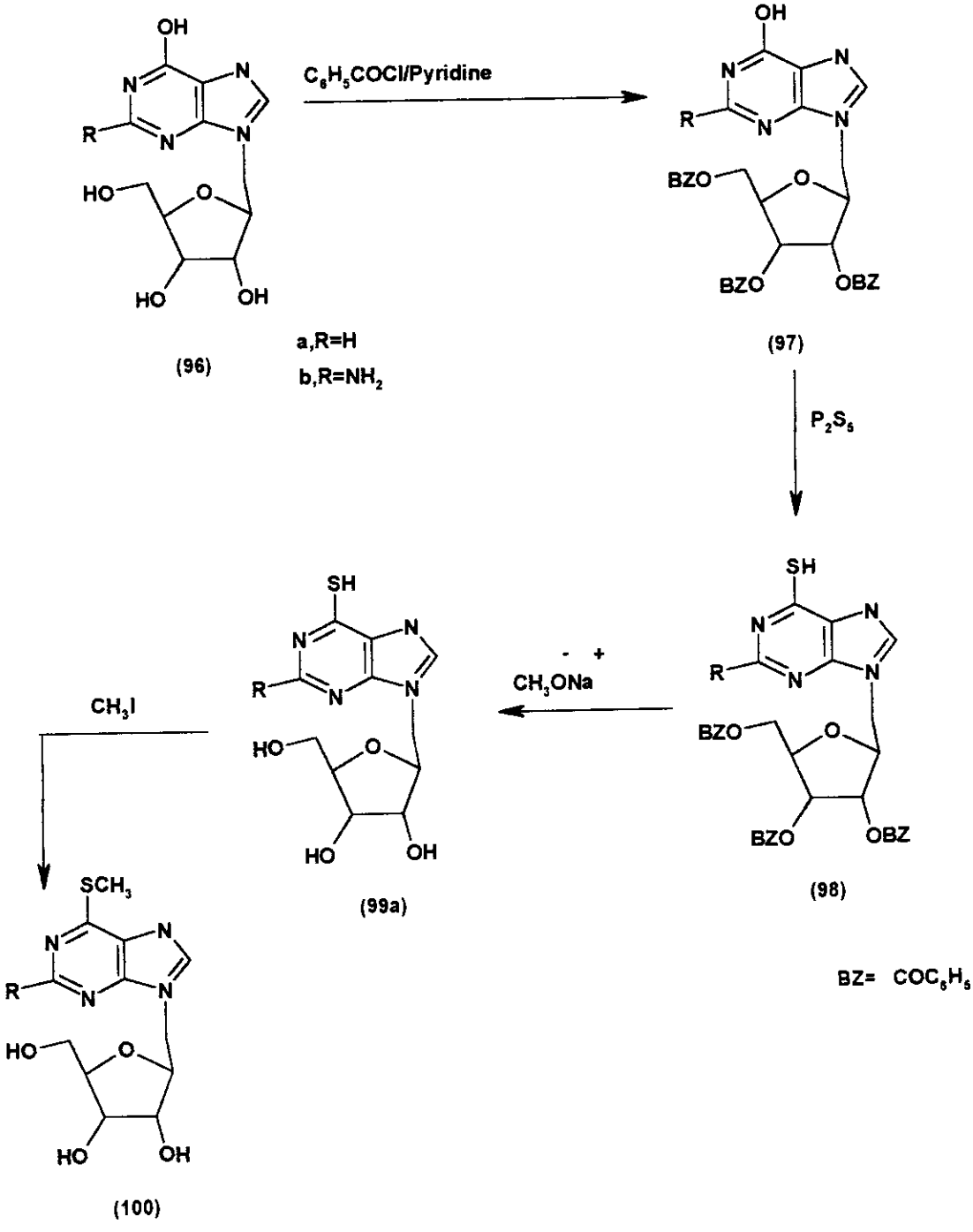
Acetylation of adenosine **(93)** followed by halogenation gave 6-iodo-9-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)purine **(94)**. Photolysis of compound **(94)** in dimethyl dimercaptide yielded 6-methylthio-9-(2,3,5-O-acetyl-β-D-ribfuranosyl) purine **(95)**.[106-111]



(93) (94) (95)

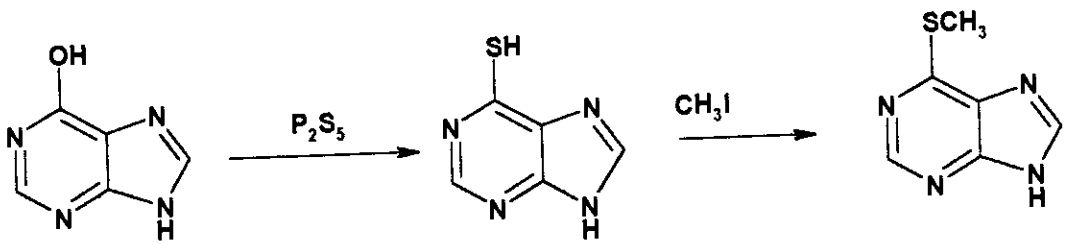
6-Mercapto -2- substituted -9- β-D-ribofuranosylpurines **(99a,b)** were synthesized by treatment of 6-hydroxy-2-substituted-9-β-D-

ribofuranosylpurines **(96)** with benzoyl chloride followed by thiation and debenzoylation. Methylation of compound **(99a)** afforded 6-methylthio-9- β-D-ribofuranosylpurine **(100)**.[112-123]



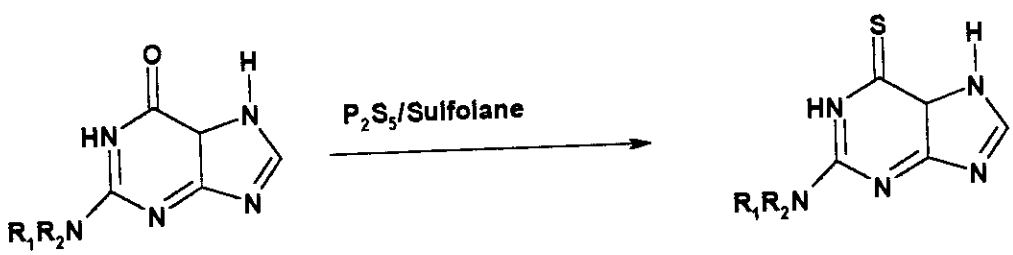
C)Imidazole derivatives with phosphorous pentasulfide

6-Methylmercaptopurine **(102b)** has been synthesized by the reaction of hypoxanthine **(101)** with phosphorous pentasulfide followed by methylation.[124-127]



(101) (102a) (102b)

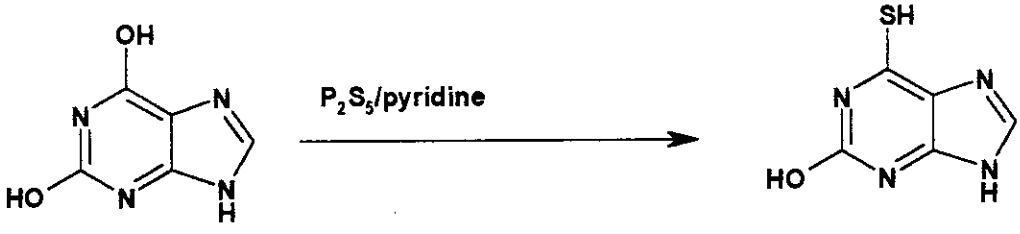
Tomsones and others.[128-132] have reported the synthesis of 6-thioguanine derivatives **(104)** by refluxing guanine derivatives **(103)** with phosphorous pentasulfide in the presence of sulfolane



(103) (104)

104	R1	R2	Yield %
a	H	CH_3	64
b	H	C_2H_5	45
c	H	C_6H_5	34
d	CH_3	CH_3	52

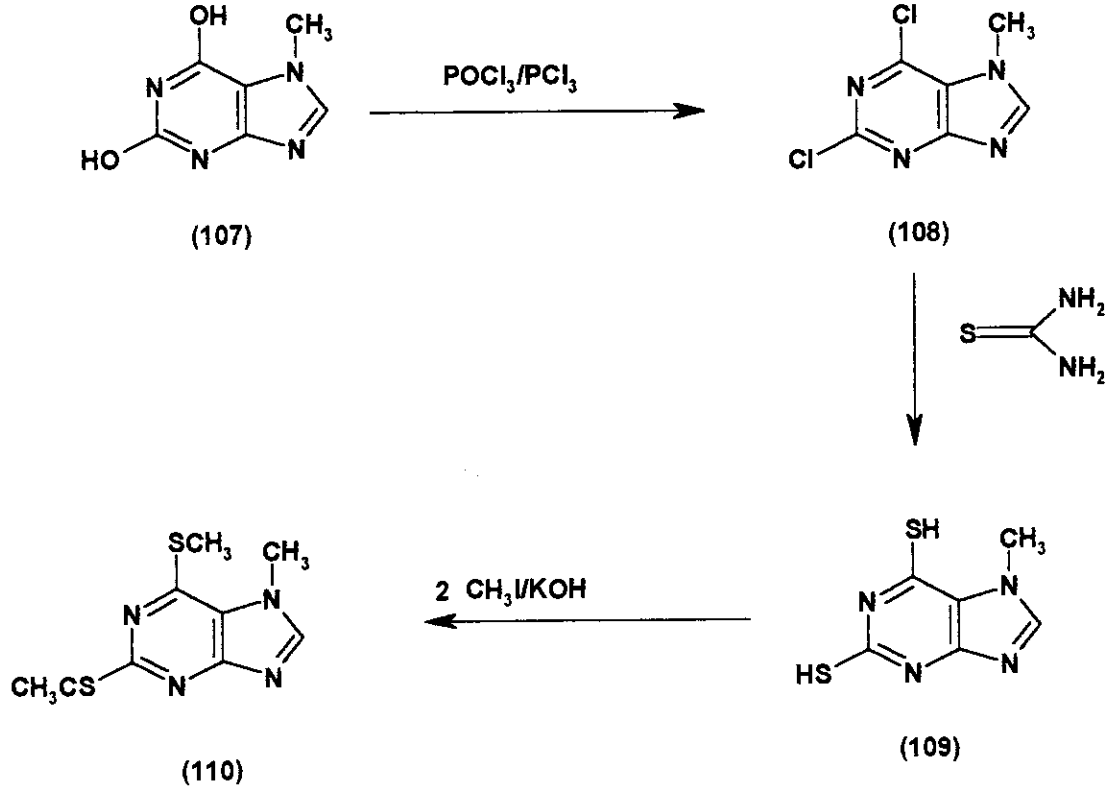
Reaction of xanthine **(105)** with phosphorous pentasulphide in refluxing pyridine yielded 2-hydroxy-6-mercaptopurine **(106)**.[57,133-135]



(105) **(106)**

d)Chlorination of Imidazo[4,5-d]pyrimidines derivatives

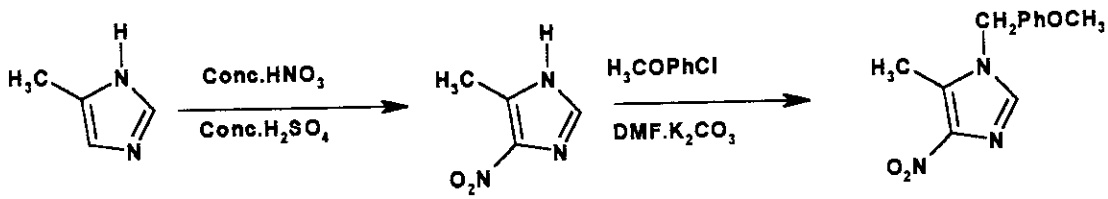
Chlorination of compound **(107)** followed by reaction with thiourea yielded 2,6-dimercapto-7-methylpurine **(110)**.[39-40]



(107) **(108)** **(109)** **(110)**

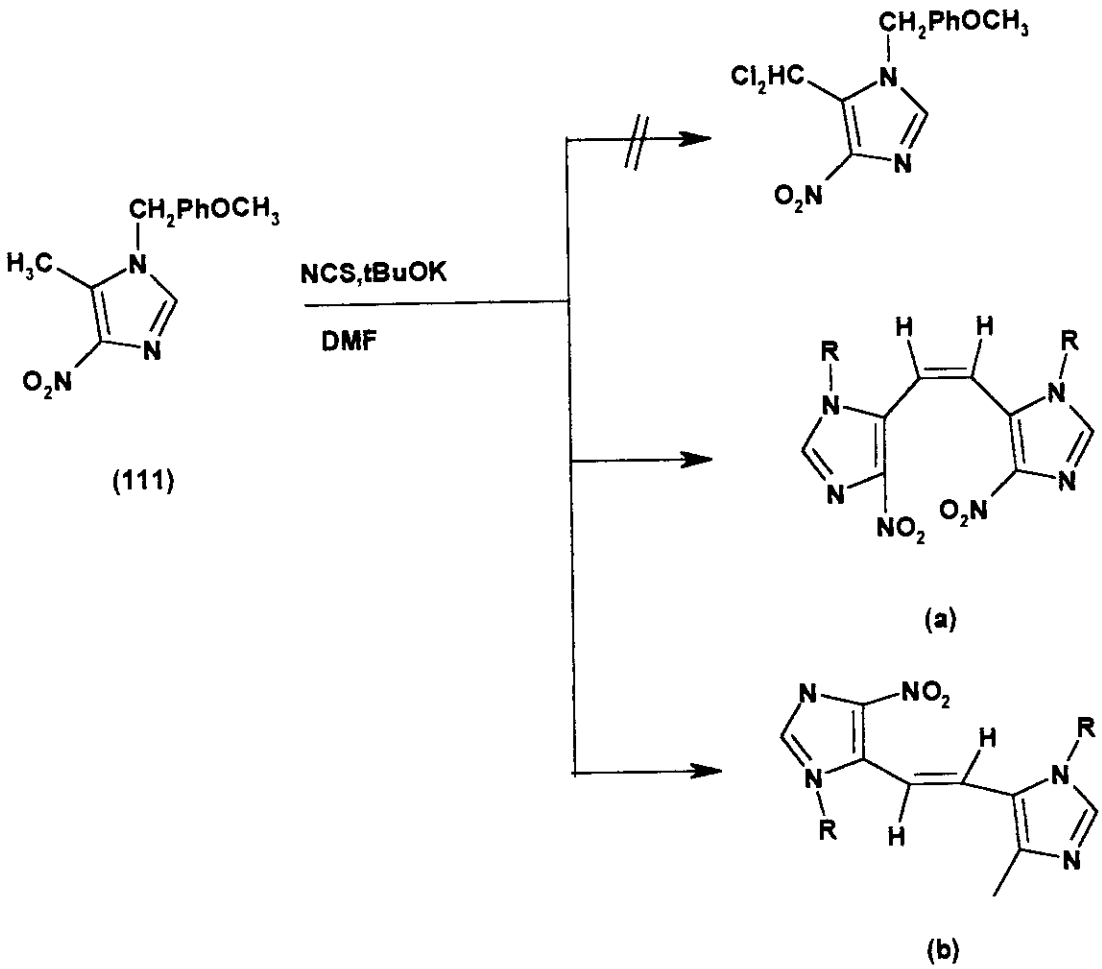
5)Novel Imidazole

The crude nitrated product was treated with *para*-methoxybenzyl chloride and potassium carbonate in DMF to yield crystals of 4-nitro-1-*p*-methoxybenzyl-5-methyl-1*H*-imidazole **(111)** as a single regioisomer, as determined from NMR data. The regioisomeric assignment of **(111)** was based upon (a) comparison of the benzyl absorptions of **(111)** in its ^{1}HNMR spectrum with those of several other benzyl-substituted nitroimidazoles,[136] and (b) the established fact that the alkylation of nitroimidazoles predominantly yield substitutions at the nitrogen atom farther away from the nitro group.[137]



(110) (111)

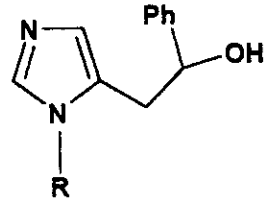
The target dimmers a and b were prepared in the following scheme by the reaction of **(111)** with *N*-chlorosuccinimide (NCS)[138] in the presence of potassium *tert*-butoxide in DMF. The same result was obtained with *N*-bromosuccinimide (NBS).


CH2PhOCH3
H3C
N
N
O2N
NCS,tBuOK
DMF
Cl2HC
CH2PhOCH3
N
N
O2N
H
H
R
N
N
N
NO2
O2N
R
N
N
(a)
N
NO2
H
R
N
N
R
H
N
N
(b)

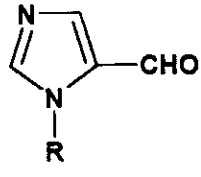
(111)

Biological activity of imidazole derivatives

Synthetic methods devoted to the preparation of new azoles are of great interest in the medicinal chemistry field because of potential biological activity of those compounds. Examples of new drugs from synthesis of azoles are, cimetidine (H_2-antihistamine) [139] clonidine (antihypertensive) [140] metronidazole (antiprotozoal) [141] clotrimazole and other antifungals [142] as well, detomidine and its methyl derivatives (valuable drugs in veterinary medicine).[143-144] Despite considerable pharmaceutical importance of imidazole derivatives and the widespread interest in their chemistry, often even simple imidazoles are not readily accessible. Most reactions include several steps, are laborious, purification is tedious and yields are often low. There is a need for additional versatile syntheses of imidazoles with specific regiochemistry and the ability to incorporate a wide variety of substituents. i.e Hydroxylethylimidazole (a) and Imidazolecarboxaldehydes(b).



(a)



(b)