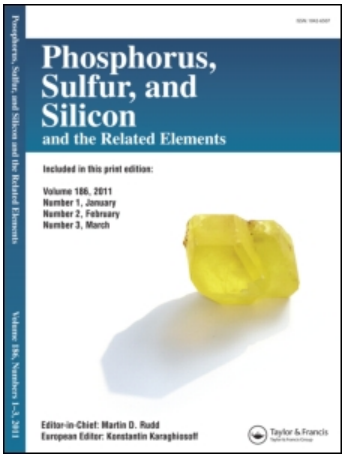

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Synthesis and Reactions of 1,1-Dimethyl-3-oxobutyl-isothiocyanate (DMO-ITC)

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SYNTHESIS AND REACTIONS OF 1,1-DIMETHYL-3-OXOBUTYL-ISOTHIOCYANATE (DMO-ITC)

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In this review an attempt has been made to compile all the existing comprehensive literature for the synthesis of 1,1-Dimethyl-3-oxobutyl-isothiocyanate (DMO-ITC) and its reactions with the compounds having different functional groups, such as amines, diamines, amino alcohols, amino phenols, amino thiophenols, amino nitriles, amino acids, and hydrazines. The peculiar behavior of the DMO-ITC is due to its sensitivity toward acids and gives different products when the reaction occurs in the absence and presence of an acid. The pH of the reaction condition also plays an important role. Normally, DMO-ITC gives pyrimidinethione derivatives when treated with amines, but reactions become interesting when the compounds have an amino group as well as the other functional group (NH_2, OH, SH, CN, COOH) at ortho position, providing condensed bicyclic, tricyclic, or poly heterocycles with ring nitrogen and/or sulfur is of biological importance. The reaction of DMO-ITC with ethylene diamine, o-*phenylenediamines, 1,2-diaminoanthraquinone,* o-*diaminonaphthalenes,* N-*aminoethyladenosine, 2-amino ethanol,* o-*aminophenols,* o-*aminothiophenols,* o-*aminobenzonitriles, and* o-*aminobenzoic acids gave imidazopyrimidinethione, pyrimidobenzimidazolethiones, pyrimidoanthraquinonimidazolethione, pyrimidonaphthoimidazolethiones, furanopurinimidazopyrimidinethione, oxazolopyrimidinethione, oxafluorenethiones, thiafluorenethiones, thioxophenanthreneones, and thiaphenanthreneones derivatives respectively. But similar reactions were not seen with* o-*diaminoheterocycles. Hydrazines derivatives gave seven-membered heterocycles, that is, triazepinethiones derivatives. The synthesis of the heterocycles are well defined in separate sections according to the update references.*

Keywords: Benzoheterocycles; non-benzoheterocycles; oxobutyl isothiocyanate; polyheterocycles

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INTRODUCTION

A large number of synthetic as well as naturally occurring isothiocyanates belonging to an important class of compounds are proved to be effective chemopreventive agents. A wide variety of isothiocyanates have been reported as potential anticancer agents.[1–15] Additionally, isothiocyanates also have been reported to exhibit other interesting biological effects such as antibacterial,[16,17] anti-HIV,[18] antimicrobiol,[19] antiplatelet,[4] analgesic,[20] anthelmintic,[21] genotoxic,[22–24] mutagenic,[16] and gastric mucosal repair.[25]

Frequent consumption of cruciferous vegetables that contain organosulfur compounds known as isothiocyanates decreases the risk in various types of cancer. This may be due to the blocking of the metabolic activation of the carcinogens by altering the enzymes involved in the process, induction of apoptosis, and detoxification of enzymes.[26] The mechanisms of the chemopreventive effects of isothiocyanates is of great importance not only because of the blocking of the formation of a wide variety of carcinogen-induced tumors in rodents, but also because of these isothiocyanates and their glucosinolate precursors which are widespread in human dietary systems and are consumed in substantial quantities. To what extent of these substances contribute to the protective effects of vegetables against cancer is unclear.[27] The mechanism of anticarcinogenic activities of isothiocyanates is thought to proceed through two distinct pathways, by tandem and cooperating mechanisms: (1) the suppression of carcinogen activation by cytochromes P-450, probably by a combination of the down-regulation of enzyme levels and direct inhibition of their catalytic activities, which thereby lower the levels of ultimate carcinogens formed and (2) the induction of phase II enzymes such as glutathione transferases and NADPH (quinone oxidoreductase) which detoxify any residual electrophilic metabolities generated by phase I enzymes and thereby destroy their ability to damage DNA.[28] Recent studies on the mechanism of cancer chemopreventive action of isothiocyanates suggested that the isothiocyanates are absorbed across intestinal cell membranes by diffusion and bind reversibly to plasma protein thiols by thiocarbamoylation. Free isothiocyanate enters into the cells and is converted into the glutathione conjugate by glutathione S-transferases. The glutathione conjugate has been exported from cells by multidrug resistance proteins and metabolized in the mercapturic acid pathway to the corresponding mercapturic acid.[29]

Present studies on the molecular mechanism of cell death induced by a cancer chemoprotective compound like benzyl isothiocyanate

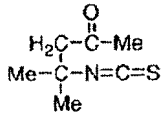
(BITC) suggested that BITC induces apoptosis through a mitochondrial redox-sensitive mechanism.[30] BITC may be expected to be metabolized to the reactive benzyl isocyanate intermediate that covalently modified the P450 apoprotein or hydrolyzed to form benzylamine.[31] Allyl isothiocyanate (AITC) is known to be more weakly carcinogenic than BITC toward the rat urinary bladder and found to be useful for the extension of shelf life by treatment in combination with acetic acid on cooked rice.[32,33] Tribenzylsilyl isothiocyanate (TBS-ITC) has been used for C-terminal peptides and proteins sequencing and successfully applied to sequence six C-terminal residues of house apomyoglobin and a synthetic peptide at low nanomole levels.[34] The chemistry involves activation with acetic acid anhydride, derivatization with TBS-ITS, and cleavage of derivatized C-terminal amino acid thiohydantoin with sodium hydroxide. The tribenzylsilyl is a bulky, electron donating group and also is a good leaving group. It facilitates the nucleophilic attack of the NCS-1 in the coupling reaction. Guanidinium isothiocyanate is proved to be a novel choice in the isolation of Mycobacterium tuberculosis DNA.[35]

It already has been recognized that an isothiocyanate may serve as a versatile building block to prepare a wide range of thioureas,[36–39] heterocycles,[40–43] and organometallic[44–46] compounds for academic, pharmaceutical, and industrial interest. The association of high electrophilicity and nucleophilicity with carbon and sulfur atoms, respectively, of the isothiocyanates and their extended π electron system make them unique precursors of a large variety of target molecules. Cycloaddition reactions of the isothiocyanates further help to generate additional heterocycles. Although a number of reviews[10,11,15,47–55] on isothiocyanates were already published, surprisingly, not a single attempt was made on a particular isothiocyanate, that is, 1,1-dimethyl-3-oxobutyl-isothiocyanate (DMO-ITC).

The chemistry of DMO-ITC has an increased applied importance due to its wide use for the synthesis of heterocycles of biological importance such as anticancer,[56–58] anti-inflammatory,[56–63] analgesic,[56,58–61] anti-HIV,[64,65] antibacterial,[64] antifungal,[64] antiamoebic,[66] and anthelmintic.[66] The importance of DMO-ITC also is supported by a large number of research publications each year. The main aim of the present review is to provide comprehensive coverage of the use of DMO-ITC to construct various heterocycles. No attempt has been made to compile all the literatures falling within the scope of this review, instead emphasis has been laid on all those publications that would help to present a broader prospective of this isothiocyanate in the synthesis of heterocycles.

SYNTHESIS OF DMO-ITC

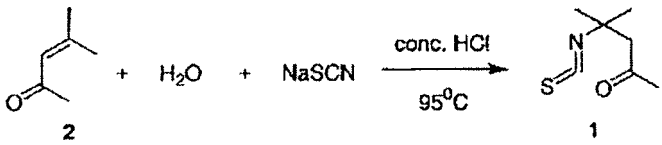
DMO-ITC was first synthesized by Herman in 1946, but at that time its structure was assigned as 2-methyl-2-thiocyanato-4-pentanone.[67] Later on the results from subsequent investigations of its reactions showed that it has the structure of 2-isothiocyanato-2-methyl-4-pentanone or 1,1-dimethyl-3-oxobutyl-isothiocyanate (DMO-ITC), which is supported by its IR[68] and NMR[69] spectras.



1 (DMO-ITC)

A number of synthetic methods already have been developed for the synthesis of DMO-ITC (**1**), which are as mentioned below.

Method-A.[67] This method involes the reaction of mesityl oxide, that is, 4-methyl-pent-3-en-2-one (**2**) with sodium thiocyanate in the presence of conc. HCl. to give DMO-ITC (**1**) in 72% of yield.



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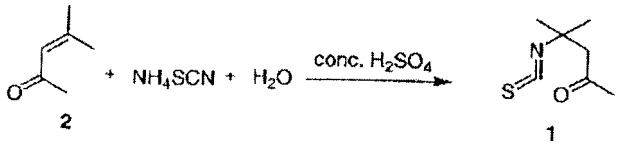
Method-B.[70] Mesityl oxide (**2**) treated with ammonium thiocyanate in the presence of conc. H_2SO_4 to generate DMO-ITC (**1**) in very good yield (92%).



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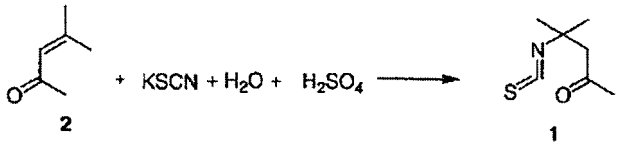
Method-C.[71] A mixture of sulphuric acid, water, and mesityl oxide (**2**) was treated with a solution of potassium thiocyanate in water to give DMO-ITC (**1**) in 69% of yield.



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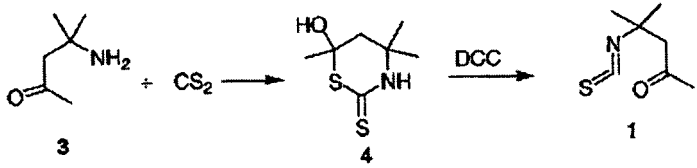
Method-D.[72] The reaction of 4-amino-4-methyl-pentan-2-one (**3**) with CS_2 to give 6-hydroxy-4,4,6-trimethyl-[1,3]thiazinane-2-thione (**4**),[73] which on treatment with DCC to give DMO-ITC (**1**) in 73% of yield.



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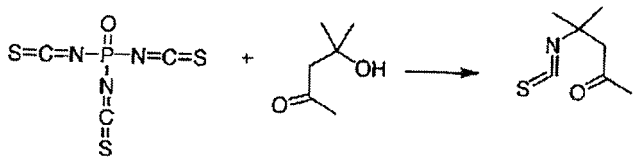
Method-E.[74] DMO-ITC (**1**) also was prepared by the reaction of acetone with the mixture of $POCl_3$ and KSCN in 63% of yield.

1

Method-F.[75] Phosphoryl isothiocyanate (**5**) reacts readily with 1,1-dimethyl-3-oxobutyl-alcohol (**6**) to give DMO-ITC (**1**) in good yield (78%).



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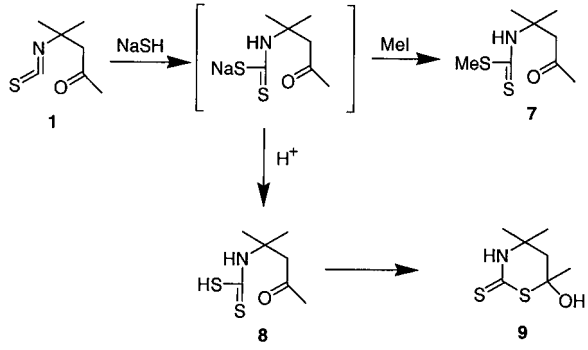
REACTIONS OF DMO-ITC

NaSH

The condensation of DMO-ITC (**1**) with NaSH gave $MeCOCH_2CMe_2NHCS_2Na$, which on reaction with MeI afforded (1,1-dimethyl-3-oxo-butyl)-dithiocarbamic acid methyl ester (**7**) and with mineral acids (1,1-dimethyl-3-oxo-butyl)-dithiocarbamic acid (**8**) as well as their ring tautomer, 6-hydroxy-4,4,6-trimethyl-[1,3]thiazine-2-thione (**9**) (Scheme 1).[76]



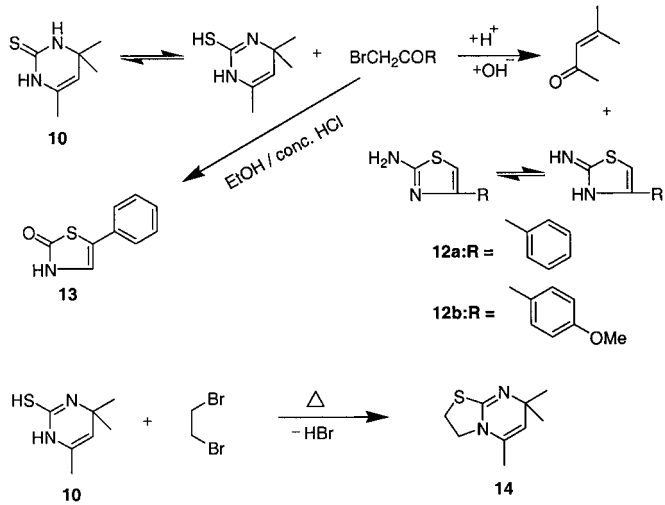
SCHEME 1

NH_4OH and $NH_2OH \cdot HCl$

DMO-ITC (**1**) when reacted with an excess of NH_4OH gave 4,4,6-trimethyl-3,4-dihydro-1*H*-pyrimidine-2-thione (**10**),[70,77] where as with $NH_2OH.HCl$, it gave 1-hydroxy-4,4,6-trimethyl-3,4-dihydro-1*H*-pyrimidine-2-thione (**11**).[78]

The condensation of 4,4,6-trimethyl-3,4-dihydro-1*H*-pyrimidine-2-thione (**10**) with ω-bromo-acetophenone and with p-methoxy-ω-bromo-acetophenone in boiling ethanol furnished solids which on treatment with base gave 2-amino-4-phenylthiazole (**12a**) and 2-amino-4-(p-methoxyphenyl)thiazole (**12b**) respectively.[79] However, when treated with phenacyl bromide in ethanol containing conc. HCl furnished 5-phenyl-3*H*-thiazol-2-one (**13**).[80] 4,4,6-Trimethyl-3,4-dihydro-1*H*-pyrimidine-2-thione (**10**) readily condensed with ethylenedibromide to give 5,7,7-trimethyl-2,3-dihydro-7*H*-thiazo[3,2-*a*]pyrimidine (**14**).[79] The formation of (**14**) by the condensation of (**10**) and ethylene dibromide shows that H attached to N at 3 is more mobile (Scheme 2).

4,4,6-Trimethyl-3,4-dihydro-1*H*-pyrimidine-2-thione (**10**) on acid catalyzed dimerization gave the dimmer 4,6,6,4′,6′,6′-hexamethyl-3,4,5,6,5′,6′-hexahydro-1*H*,1′*H*-[4,5′]bipyrimidinyl-2,2′-dithione (**15**)[81] whereas on heating with HCl or H_2SO_4 at 100–110°C gave thiourea, 2-amino-4,6,6-trimethyl-6*H*-[1,3]thiazine (**16**), and 4,6,6-trimethyl-6-(4′,6′,6′-trimethyl-1′,4′-dihydropyrimidin-2′-ylsulfanyl)-tetrahydropyrimidine-2(1*H*)-thione (**17**).[82] Compound (**10**) on condensation with

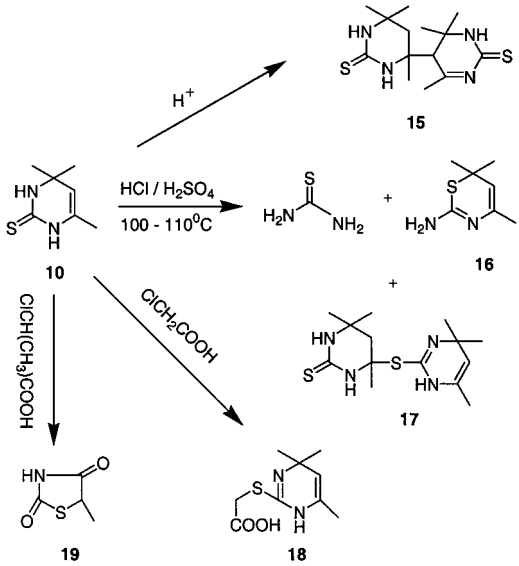


SCHEME 2

chloroacetic acid gave (4,4,6-trimethyl-1,4-dihydro-pyrimidin-2-ylsulfanyl)-acetic acid (**18**), and, with 2-chloropropionic acid, gave 5-methyl-thiazolidine-2,4-dione (**19**)[80] (Scheme 3).

Aliphatic Amines

The condensation of DMO-ITC (**1**) with n-propylamine at 5–8°C in the presence of water gave 2-mercapto-4,6,6-trimethyl-3-propyl-3,4,5,6-tetrahydro-pyrimidin-4-ol (**20**),[83] but with cyclohexylamine and isopropylamine in the presence of water and H_2SO_4 at 85°C gave 1-cyclohexyl-4,4,6-trimethyl-1,4-dihydro-pyrimidine-2-thiol (**21a**) and 1-isopropyl-4,4,6-trimethyl-1,4-dihydro-pyrimidine-2-thiol (**21b**) respectively.[77] An aqueous solution of alkylamine treated with DMO-ITC (**1**) in the presence of HCl and refluxed gave 1-alkyl-4,4,6-trimethyl-1,4-dihydro-pyrimidine-2-thiol (**22**)[68] but in the case of two amines, that is, methylamine and allylamine, the initially obtained products were the intermediate 1-(1,1-dimethyl-3-oxobutyl)-3-methyl thiourea (**23a**) and 1-allyl-3(1,1-dimethyl-3-oxobutyl)-thiourea (**23b**), which on heating with excess of 25% H_2SO_4, ring closure was effected to give the corresponding pyrimidines, 1,4,4,6-tetramethyl-3,4-dihydro-1*H*-pyrimidine-2-thione (**24a**) and 1-allyl-4,4,6-trimethyl-3,4-dihydro-1*H*-pyrimidine-2-thione (**24b**).[68] Condensation of DMO-ITC (**1**) with n-pentylamine and 3-(decyloxy)propylamine in an organic

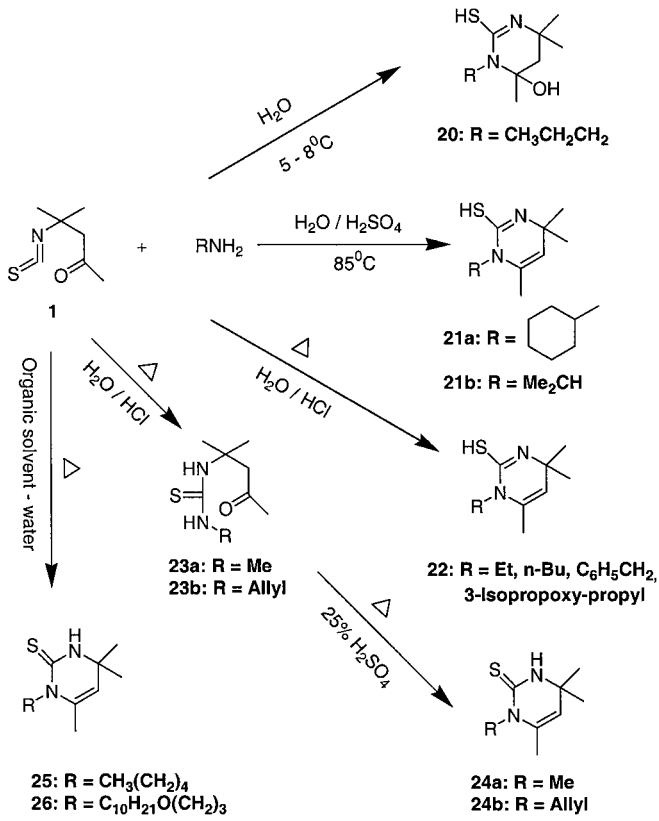


SCHEME 3

solvent-water mixture with simultaneous azeotropic distillation gave 4,6,6-trimethyl-1-pentyl-3,4-dihydro-1*H*-pyrimidine-2-thione (**25**)[84] and 1-[3-(decyloxy)propyl]-4,4,6-trimethyl-3,4-dihydro-1*H*-pyrimidine-2-thione (**26**)[85] respectively (Scheme 4).

In aqueous acidic media a slow conversion of 1,4,4,6-tetramethyl-3,4-dihydro-1*H*-pyrimidine-2-thione (**24a**) to 6-hydroxy-1,4,4,6-tetramethyl-tetrahydro-pyrimidine-2-thione (**27**) and of their corresponding *s*-alkylated derivative was observed.[86] Compounds (**24a**) and (**27**) were *s*-alkylated with MeI, EtBr, BzCl, and $CH_2ClCOOH$ in Me_2CO. Hydrogen halides of *s*-alkylated (**24a**) and (**27**) were converted into corresponding free bases (**28**) and (**29**) respectively[86] at 0°C with aqueous NH_3. When compound (**24a**) was treated with aqueous chloroacetic acid and 2-chloropropionic acid, it gave the corresponding 3-methyl-thiazolidine-2,4-dione (**30a**)[80] and 3,5-dimethyl-thiazolidine-2,4-dione (**30b**).[80,87] However, treatment with phenacyl bromide gave 3-methyl-5-phenyl-3*H*-thiazol-2-one (**31**)[80] (Scheme 5).

1-Alkyl-6-hydroxy-4,4,6-trimethyl-1,4,4,6-tetrahydro-pyrimidine-2-thione (**27a**) treated with Ac_2O containing H_2SO_4 afforded the corresponding 1-alkyl-4,4,6-trimethyl-3,4-dihydro-1*H*-pyrimidine-2-thione (**24**), which rearranged in the presence of conc. HCl, forming the corresponding alkyl-(4,4,6-trimethyl-3,4-dihydro-[1,3]thiazin-2-ylidene)-amine (**32**).[88] 1-Alkyl/alkenyl-4,4,6-trimethyl-3,4-dihydro-1*H*-pyrimidine-2-thione (**24**) when heated in 11M–HCl at 95–100°C

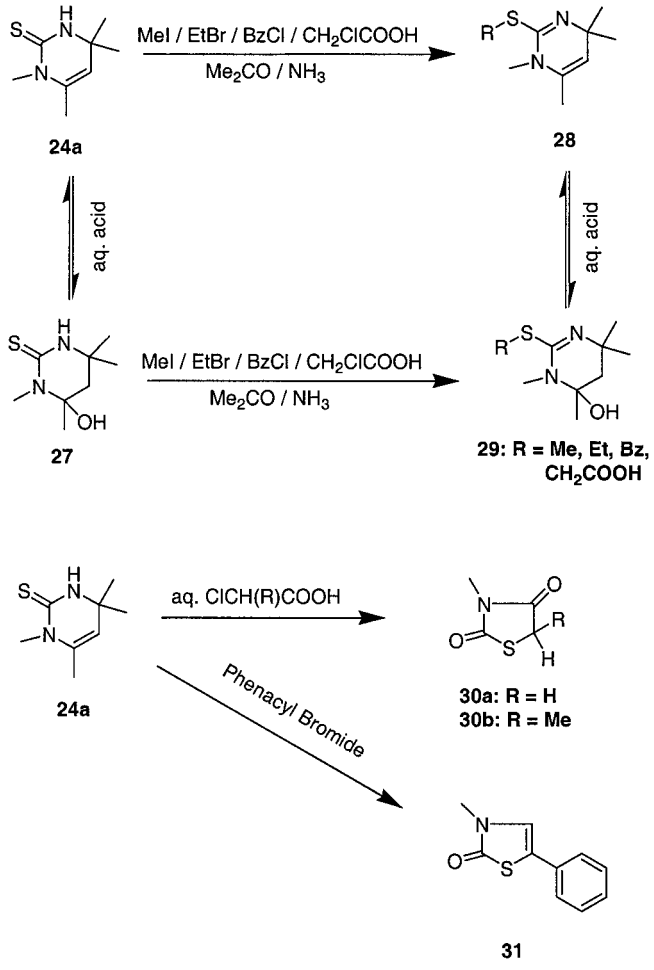


SCHEME 4

gave corresponding alkyl/alkenyl-(4,4,6-trimethyl-4*H*-[1,3]thiazin-2-yl)-amine (**33**),[89] but at 100–110°C gave alky/alkenyl thiourea (**34**)[89,90] (Scheme 6).

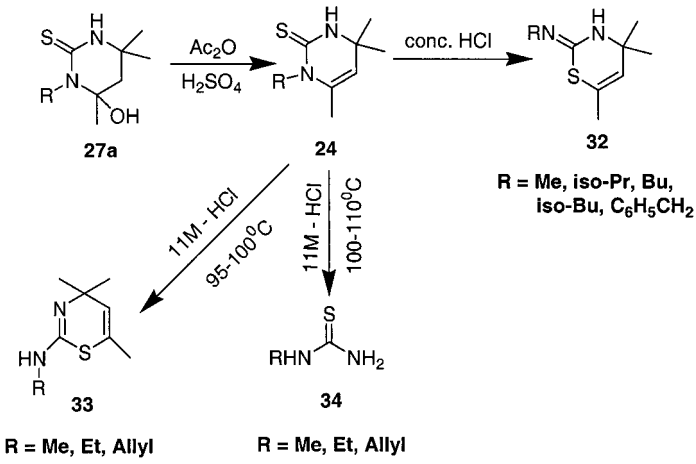
1-Alkyl/alkenyl-4,4,6-trimethyl-3,4-dihydro-1*H*-pyrimidine-2-thione (**24**) when heated in an inert medium causes rearrangement to 4-alkyl/alkenylamino-6,6-dimethyl-5,6-dihydro-1*H*-pyridine-2-thione (**35**), which on the treatment with H_2O_2 in the presence of KOH is converted into their corresponding 4-alkyl/alkenylamino-6,6-dimethyl-5,6-dihydro-1*H*-pyridine-2-one (**36**) and can be reconverted into (**35**) by treating with P_4S_{10}. Pyridinethione (**35**) reacts with alkyl halides to give 4-alkyl/alkenylamino-2-alkylthio- 6,6-dimethyl-5,6-dihydropyridine hydroiodide or bromide (**37**) and (**38**) (Scheme 7).[91]

Dichlorocarbene on reaction with 1-alkyl-4,4,6-trimethyl-3,4-dihydro-1*H*-pyrimidine-2-thione (**24**) formed 7,7-dichloro-3-dichloromethylthio-2-alkyl-1,5,5-trimethyl-2,4-diaza-bicyclo[4.1.0]hept-3-ene

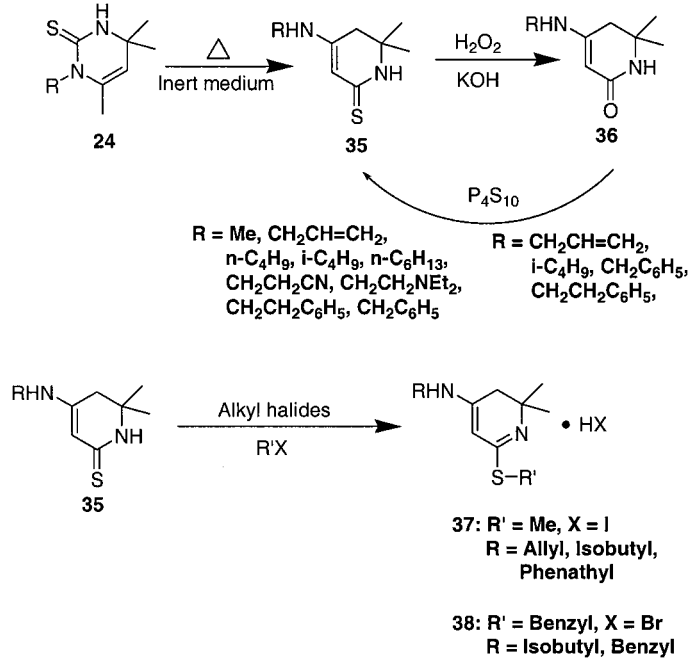


SCHEME 5

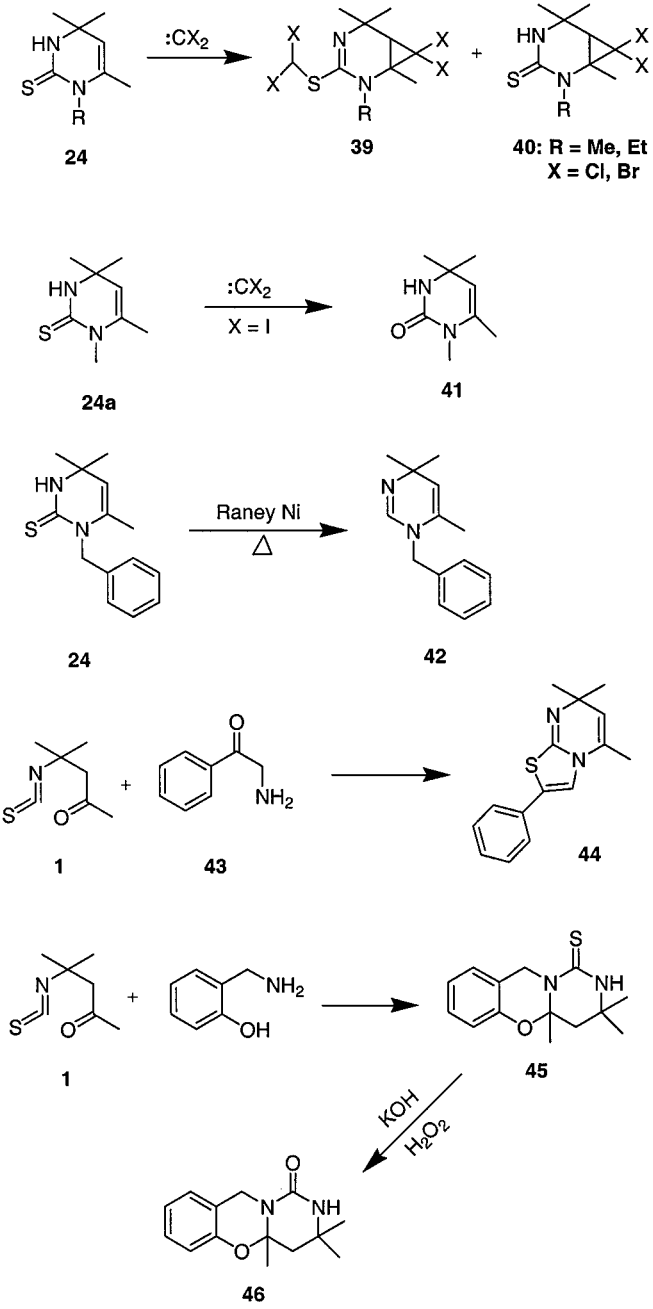
(**39**) and 7,7-dichloro-2-alkyl-1,5,5-trimethyl-2,4-diaza-bicyclo[4.1.0]-heptane-3-thione (**40**).[92,93] On heating as such or under acidic or basic conditions (**39**) changed to the corresponding (**40**) quantitatively. Reaction with dibromocarbene gave the corresponding bromo derivatives. But 1,4,4,6-tetramethyl-3,4-dihydro-1*H*-pyrimidine-2-thione (**24a**) treated with diiodocarbene formed the corresponding 1,4,4,6-tetramethyl-3,4-dihydro-1*H*-pyrimidin-2-one (**41**).[93] 1-Benzyl-4,4,6-trimethyl-3,4-dihydro-1*H*-pyrimidine-2-thione (**24**) when warmed with



SCHEME 6



SCHEME 7



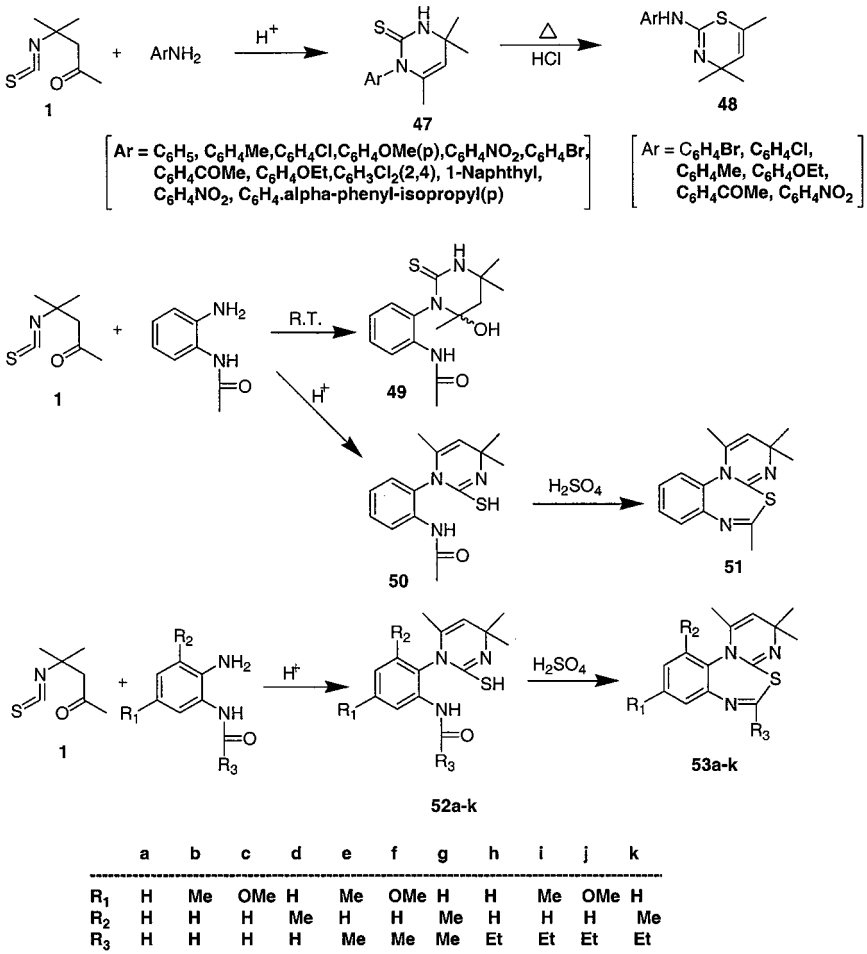
SCHEME 8

Raney nickel, desulfurization occurred to form 1-benzyl-4,4,6-trimethyl-1,4-dihydro-pyrimidine (**42**).[94] DMO-ITC (**1**) reacted with α-aminoketone, that is, 2-amino-1-phenyl-ethanone (**43**), gave 5,7,7-trimethyl-2-phenyl-7*H*-thiazolo[3,2-*a*]pyrimidine (**44**).[95] Further reaction of DMO-ITC (**1**) with *o*-hydroxy benzylamine gave condensed heterocycle, that is, 3,3,4a-trimethyl-2,3,4,4a-tetrahydro-9*H*-10-oxa-2,9a-diaza-anthracene-1-thione (**45**), which on the treatment with H_2O_2/KOH is converted into 3,3,4a-trimethyl-2,3,4,4a-tetrahydro-9*H*-10-oxa-2,9a-diaza-anthracene-1-one (**46**)[96] (Scheme 8).

Aromatic Amines

Condensation of DMO-ITC (**1**) with aromatic amines in the presence of an acid afforded 1-aryl-4,4,6-trimethyl-3,4-dihydro-1*H*-pyrimidine-2-thiones (**47**),[68,70,77,97,98] which on heating with conc. HCl get rearranged to aryl-(4,4,6-trimethyl-4*H*-[1,3]thiazin-2-yl)-amines (**48**).[88,98] The condensation of *o*-amino acetanilide with DMO-ITC (**1**) at room temperature gave *N*-[2-(6-hydroxy-4,4,6-trimethyl-2-thioxo-tetrahydro-pyrimidin-1-yl)phenyl]-acetanilide (**49**)[60] where as on refluxing in the presence of catalytic amount of an acid gave *N*-[2-(2-mercapto-4,4,6-trimethyl-4*H*-pyrimidin-1-yl)-phenyl]-acetanilide (**50**) which was cyclized to 1,3,3,6-tetramethyl-3*H*-5-thia-4,7,11b-triaza-dibenzo[*a,c*]cycloheptene (**51**).[99] Similarly, the other amides, that is, *N*-(2-amino-phenyl or aryl)-formamides, *N*-(2-amino-aryl)-acetamides, and *N*-(2-amino-phenyl or aryl)-propionamides treated with DMO-ITC (**1**) gave *N*-[2-(2-mercapto-4,4,6-trimethyl-4*H*-pyrimidin-1-yl)-phenyl or aryl]-formamides, *N*-[2-(2-mercapto-4,4,6-trimethyl-4*H*-pyrimidin-1-yl)-aryl]-acetamides, and *N*-[2-(2-mercapto-4,4,6-trimethyl-4*H*-pyrimidin-1-yl)-phenyl or aryl]-propionamides (**52a–k**) respectively. The products (**52a–k**) were cyclized to 1,3,3-trimethyl-3*H*-5-thia-4,7,11b-triaza-dibenzo[*a,c*]cycloheptene, 1,3,3,6-tetramethyl-3*H*-5-thia-4,7,11b-triaza-dibenzo[*a,c*]cycloheptene, and 6-ethyl-1,3,3-trimethyl-3*H*-5-thia-4,7,11b-triaza-dibenzo[*a,c*]cycloheptene derivatives (**53a–k**) respectively[99] (Scheme 9).

4,4,6-Trimethyl-1-(2-nitroaryl and 4-nitrophenyl or phenyl)-3,4-dihydro-1*H*-pyrimidine-2-thiones (**55a–f**) were obtained by the condensation of corresponding amines (**54a–f**) with DMO-ITC (**1**) in the presence of an acid. (**55a–c**) on reduction with Al/Hg amalgam gave 1-(2-aminoaryl)-4,4,6-trimethyl-3,4-dihydro-1*H*-pyrimidine-2-thiones (**56a–c**).[63] The reduction of the compounds (**55a–f**) with $SnCl_2$/HCl at room temperature gave 1-(2-aminoaryl or 4-aminophenyl or phenyl)-6-hydroxy-4,4,6-trimethyl-tetrahydro pyrimidine-2-thiones

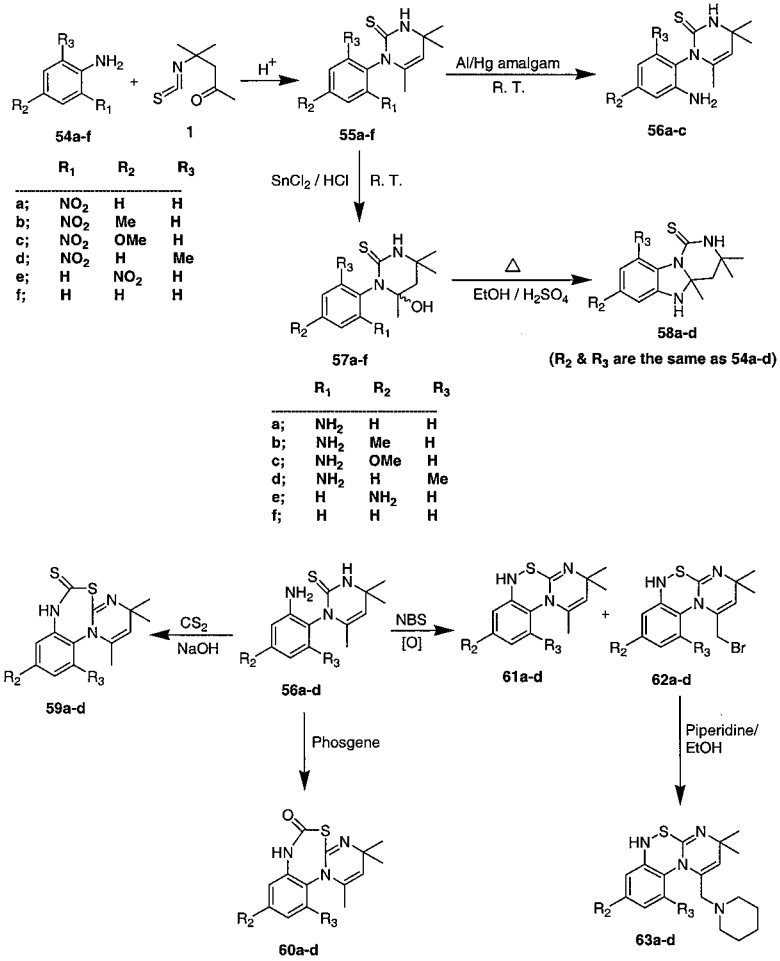


	a	b	c	d	e	f	g	h	i	j	k
R_1	H	Me	OMe	H	Me	OMe	H	H	Me	OMe	H
R_2	H	H	H	Me	H	H	Me	H	H	H	Me
R_3	H	H	H	H	Me	Me	Me	Et	Et	Et	Et

SCHEME 9

(**57a–f**)[63] whereas at lower temperature (i.e., below 10°C) (**56a–d**).[100] 1-(2-Aminoaryl)-6-hydroxy-4,4,6-trimethyl-tetrahydro pyrimidine-2-thiones (**57a–d**) undergo cyclization to give 3,3,4a-trimethyl-3,4,4a,5-tetrahydro-2*H*-benzo[4,5]imidazo[1,2-*c*]pyrimidine-1-thione derivatives (**58a–d**)[63] when refluxed in ethanol using a catalytic amount of sulfuric acid. 1-(2-Aminoaryl)-4,4,6-trimethyl-3,4-dihydro-1*H*-pyrimidine-2-thiones (**56a–d**) gave 1,3,3-trimethyl-3*H*, 7*H*-5-thia-4,7,11b-triaza-dibenzo[*a,c*]cycloheptene-6-thiones (**59a–d**) and 1,3, 3-trimethyl-3*H*, 7*H*-5-thia-4, 7, 11b-triaza-dibenzo[*a,c*] cycloheptene-6-ones (**60a–d**) on condensation with carbon disulphide and

phosgene respectively.[100] The oxidative cyclization of thiones (**56a–d**) with Br_2, I_2, or H_2O_2 gave a single product 2,2,4-trimethyl-2*H*, 9*H*-10-thia-1,4a,9-triaza-phenantherene derivatives (**61a–d**) while with *N*-bromosuccinimide gave two products 2,2,4-trimethyl-2*H*, 9*H*-10-thia-1,4a,9-triaza-phenantherene derivatives (**61a–d**) and 4-bromomethyl-2,2-dimethyl-2*H*, 9*H*-10-thia-1,4a,9-thiaza-phenanthere derivatives (**62a–d**). Bromo derivatives (**62a–d**) treated with piperidine gave bromine free products 2,2-dimethyl-4-piperidin-1-ylmethyl-2*H*, 9*H*-10-thia-1,4a,9-triaza-phenanthrene derivatives (**63a–d**)[101] (Scheme 10).

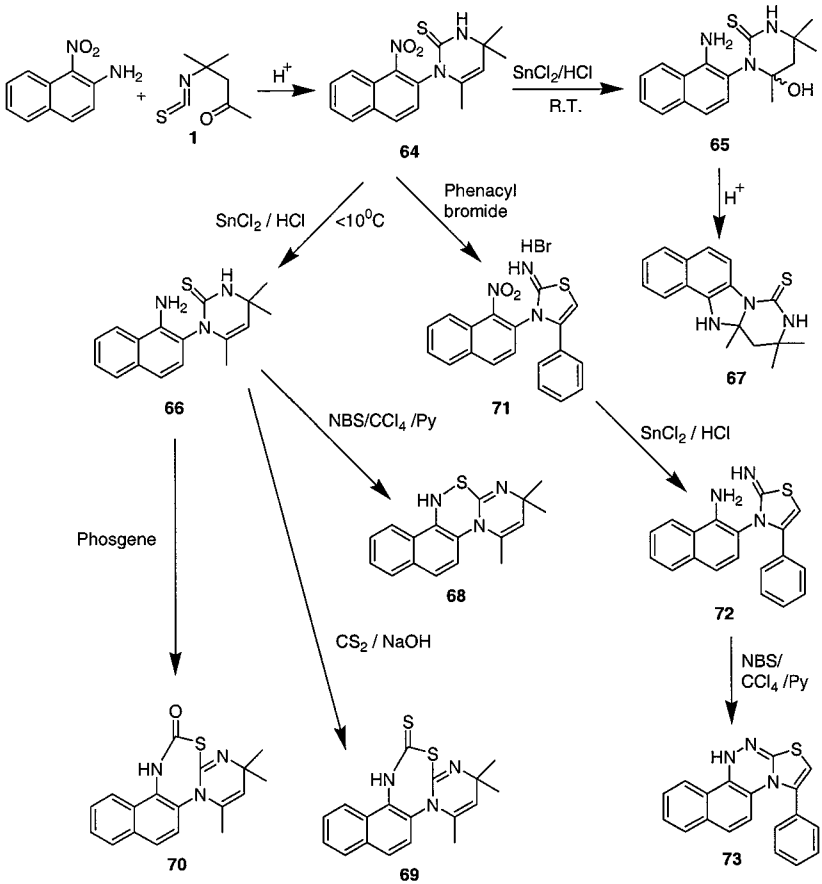


	R_1	R_2	R_3
a;	NO_2	H	H
b;	NO_2	Me	H
c;	NO_2	OMe	H
d;	NO_2	H	Me
e;	H	NO_2	H
f;	H	H	H

	R_1	R_2	R_3
a;	NH_2	H	H
b;	NH_2	Me	H
c;	NH_2	OMe	H
d;	NH_2	H	Me
e;	H	NH_2	H
f;	H	H	H

SCHEME 10

1-Nitro-2-naphthylamine when condensed with DMO-ITC (**1**) in the presence of an acid gave 4,4,6-trimethyl-1-(1-nitro-naphthalen-2-yl)-3,4-dihydro-1*H*-pyrimidine-2-thione (**64**), which on reduction with $SnCl_2$/HCl at room temperature gave 1-(1-amino-naphthalen-2-yl)-6-hydroxy-4,4,6-trimethyl-tetrahydro-pyrimidine-2-thione (**65**)[61] where as at a lower temperature (i.e., below 10°C) gave 4,4,6-trimethyl-1-(1-amino-naphthalen-2-yl)-3,4-dihydro-1*H*-pyrimidine-2-thione (**66**).[102] Thione (**65**) undergoes cyclization in the presence of an acid gave 9,9,10a-trimethyl-9,10,10a,11-tetrahydro-8*H*-6b,8,11-triaza-benzo[*a*]fluorine-7-thione (**67**).[61] The oxidative cyclization of the reduced product (**66**) with NBS/CCl_4/pyridine gave 2,2,4-trimethyl-2*H*,11*H*-12-thia-1,4a,11-triaza-chrysene (**68**),[102]

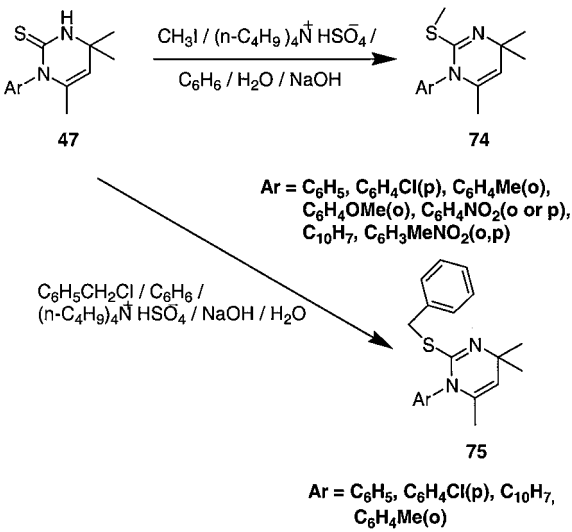


SCHEME 11

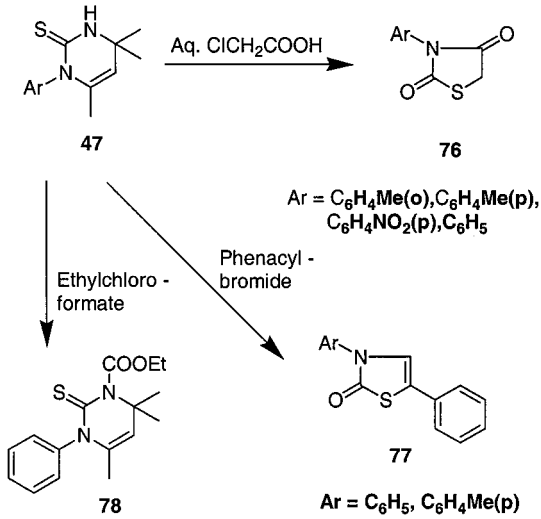
whereas with carbon disulphide and phosgene gave 2,2,4-trimethyl-2*H*,11*H*-13-thia-1,4a,11-triaza-benzo[3,4]cyclohepta[1,2-*a*]-naphthalene-12-thione (**69**) and 2,2,4-trimethyl-2*H*,11*H*-13-thia-1,4a,11-triaza-benzo[3,4]cyclohepta[1,2-*a*]naphthalene-12-one (**70**) respectively.[100] 4,4,6-Trimethyl-1-(1-nitro-naphthalen-2-yl)-3,4-dihydro-1*H*- pyrimidine-2-thione (**64**) condensed with phenacyl bromide via Michael Retrogression yielded 3-(1-nitro-naphthalen-2-yl)-4-phenyl-3*H*-thiazol-2-ylideneamine hydrobromide (**71**) which was smoothly reduced with $SnCl_2$/HCl to 3-(1-amino-naphthalen-2-yl)-2-imino-4-phenyl-2,3-dihydro-thiazole (**72**). Oxidative cyclization of (**72**) with NBS/CCl_4 in the presence of pyridine afforded 15-phenyl-11*H*-17-thia-11,12,14-triaza-cyclopenta[*a*]phenanthrene (**73**)[102] (Scheme 11).

1-Aryl-4,4,6-trimethyl-3,4-dihydro-1*H*-pyrimidine-2-thiones (**47**) was easily S-methylated and also S-benzylated under the same phase transfer conditions using methyl iodide and benzyl chloride, respectively,[103] to give 4,4,6-trimethyl-2-methylsulfanyl-1-aryl-1,4-dihydro-pyrimidines (**74**) and 2-benzylsulfanyl-4,4,6-trimethyl-1-aryl-1,4-dihydro-pyrimidines (**75**) (Scheme 12).

The pyrimidine derivatives (**47**) when treated with aqueous chloroacetic acid gave 3-aryl-thiazolidine-2,4-diones (**76**).[80,87] On the other hand, treatment with phenacyl bromide and ethyl chloroformate gave 3-aryl-5-phenyl-3*H*-thiazol-2-ones (**77**) and 4,4,6-trimethyl-3-phenyl-2-thioxo-3,6-dihydro-2*H*-pyrimidine-1-carboxylic acid ethyl ester (**78**) respectively[80] (Scheme 13).



SCHEME 12

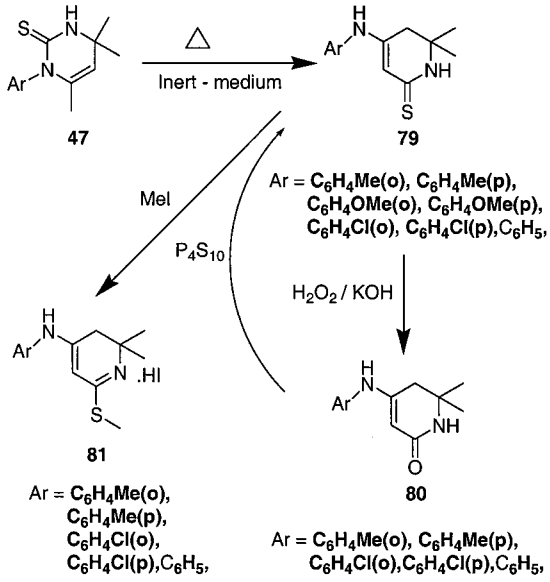


SCHEME 13

1-Aryl-4,4,6-trimethyl-3,4-dihydro-1*H*-pyrimidine-2-thiones (**47**) when heated in an inert medium causes rearrangement to 4-arylamino-5,6-dihydro-6,6-dimethyl-1*H*-pyridin-2-thiones (**79**), which was found to be converted into their respective 4-arylamino-5,6-dihydro-6,6-dimethyl-1*H*-pyridin-2-ones (**80**) by the treatment with H_2O_2 in the presence of KOH and it can be reconverted into (**79**) by treating with P_4S_{10}. Pyridine thiones (**79**) when reacted with methyl iodide afford 4-arylamino-2-methylthio-5,6-dihydro-6,6-dimethylpyridines hydroiodide (**81**)[91] (Scheme 14).

1-Phenyl-4,4,6-trimethyl-3,4-dihydro-1*H*-pyrimidine-2-thione (**47**) when heated in 11M—HCl at 95–100°C gave phenyl-(4,4,6-trimethyl-4*H*-[1,3]thiazin-2-yl)-amine (**82**), but at 100–110°C a different product phenyl-(4,4,6-trimethyl-6*H*-[1,3]thiazin-2-yl)-amine (**83**) was obtained.[82,89] On the other hand when pyrimidine thione (**47**) was warmed with Raney nickel, it desulfurized and formed 1-phenyl-4,4,6-trimethyl-1,4-dihydro-pyrimidine (**84**)[94] (Scheme 15).

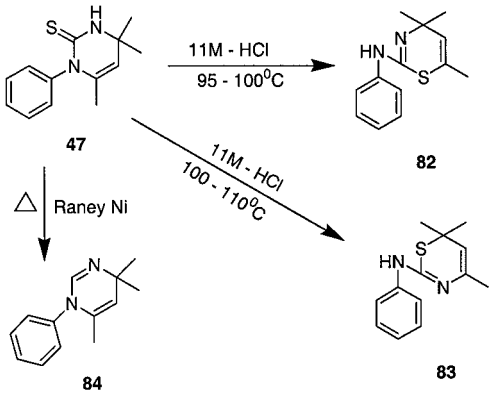
7,7-Dichloro-3-dichloromethylthio-2-aryl-1,5,5-trimethyl-2,4-diazabicyclo[4.1.0]hept-3-ene (**85**) and 7,7-dichloro-2-aryl-1,5,5-trimethyl-2,4-diazabicyclo[4.1.0]heptane-3-thione (**86**) were obtained by the treatment of pyrimidine thiones (**47**) with dichlorocarbene.[92,93] On heating as such or under acidic or basic conditions, (**85**) was converted into corresponding (**86**). Reaction with dibromocarbene gave the corresponding bromo derivatives, but when 1-phenyl-4,4,6-trimethyl-3,4-dihydro-1*H*-pyrimidine-2-thione (**47**) reacted with diiodocarbene,



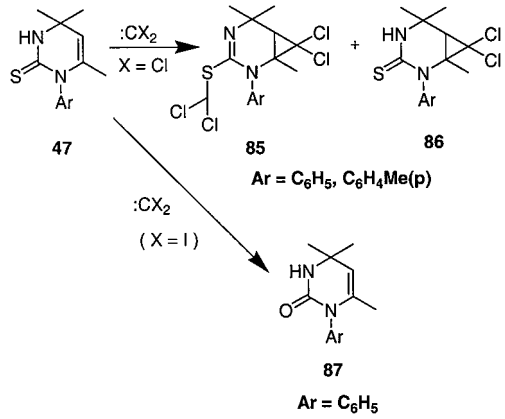
SCHEME 14

the product was 1-phenyl-4,4,6-trimethyl-3,4-dihydro-1*H*-pyrimidine-2-one (**87**)[93] (Scheme 16).

The condensation of various (2-amino-4,5-methylenedioxybenzyl-idene)amines (**88**) with DMO-ITC (**1**) gave (1,3,3-trimethyl-3*H*,6*H*-8,10-dioxa-5-thia-4,11b-diaza-cyclopenta[*b*]phenanthren-6-yl)amino derivatives (**89**). It is quite interesting to note that the compound (**89**) on

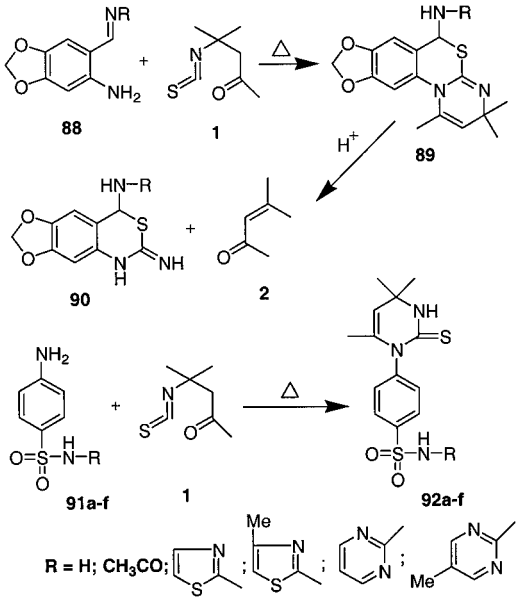


SCHEME 15



SCHEME 16

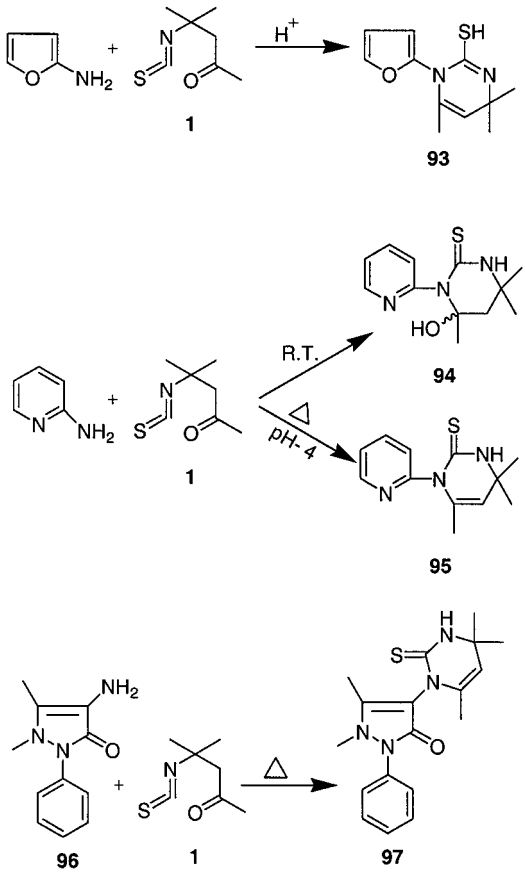
the treatment with ethanolic HCl undergo retrogression gave (6-imino-5,8-dihydro-6*H*-1,3-dioxa-7-thia-5-aza-cyclopenta[*b*]naphthalene-8-yl)-amino derivatives (**90**) and mesityl oxide.[104] Condensation of sulfathiazols (**91a–f**) with DMO-ITC (**1**) in the presence of an acid gave the corresponding *N*-substituted-4-(4,4,6-trimethyl-2-thioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-benzenesulfonamides (**92a–f**)[58] (Scheme 17).



SCHEME 17

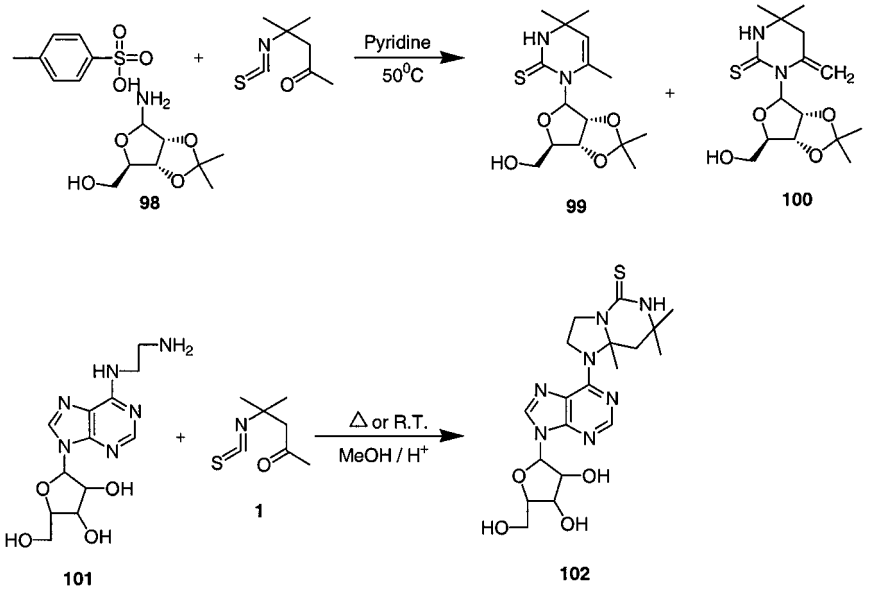
Heterocyclic Amines

DMO-ITC (**1**) on condensation with furfurylamine in the presence of an acid gave 1-furan-2-yl-4,4,6-trimethyl-1,4-dihydro-pyrimidine-2-thiol (**93**).[68] 2-Amino-pyridine on condensation with DMO-ITC (**1**) in methanol at room temperature gave 6-hydroxy-4,4,6-trimethyl-1-pyridin-2-yl-tetrahydro-pyrimidine-2-thione (**94**), while at reflux temperature of methanol in an acidic condition (pH = 4) the product was 4,4,6-trimethyl-1-pyridin-2-yl-3,4-dihydro-1*H*-pyrimidine-2-thione (**95**).[61] DMO-ITC (**1**) condensed smoothly with 4-amino-antipyrine (**96**) gave 1,5-dimethyl-2-phenyl-4-(4,4,6-trimethyl-2-thioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-1,2-dihydro-pyrazol-3-one (**97**)[59] (Scheme 18).



SCHEME 18

Reaction of 2,3-*o*-isopropylidene-ribofuranosylamine tosylate (**98**) with DMO-ITC (**1**) in dry pyridine at 50°C gave a mixture of two nucleosides, 1-(6-hydroxymethyl-2,2-dimethyl-tetrahydro-furo[3,4-*d*] [1,3]dioxol-4-yl)-4,4,6-trimethyl-3,4-dihydro-1*H*-pyrimidine-2-thione (**99**) and 1-(6-hydroxymethyl-2,2-dimethyl-tetrahydro-furo[3,4-*d*] [1,3]-dioxol-4-yl)-4,4-dimethyl-6-methylene-tetrahydro-pyrimidine-2-thione (**100**).[105] 2-[6-(2-Amino-ethylamino)-purin-9-yl]-5-hydroxymethyl-tetrahydro-furan-3,4-diol or *N*-aminoethyladenosine (**101**)[106] was condensed with DMO-ITC (**1**) either at room temperature or in refluxing methanol at pH = 5 to give 1-[9-(3,4-dihydroxy-5-hydroxymethyl-tetrahydro-furan-2-yl)-9*H*-purin-6-yl]-7,7,8a-trimethyl-hexahydro-imidazo[1,2-*c*] pyrimidine-5-thione (**102**)[57] (Scheme 19).

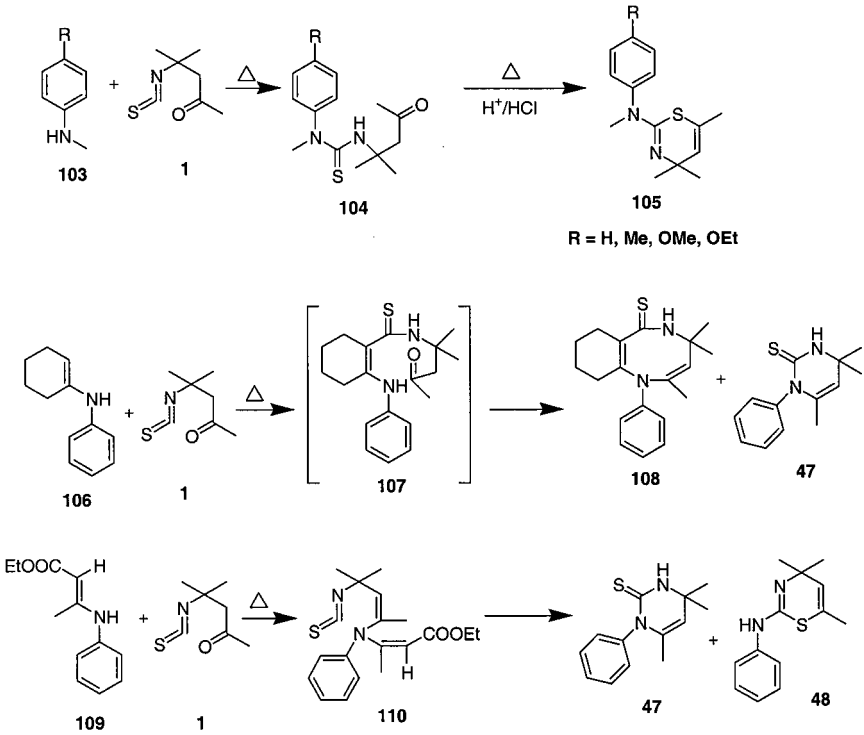


SCHEME 19

Secondary Amines

DMO-ITC (**1**) when condensed with arylmethylamines (**103**) gave 3-(1,1-dimethyl-3-oxo-butyl)-1-methyl-1-aryl-thioureas (**104**) which was cyclized by the influence of HCl to give the respective aryl-methyl-(4,4,6-trimethyl-4*H*-[1,3]thiazin-2-yl)-amines (**105**).[98] The condensation of cyclohex-1-enylaniline (**106**) with DMO-ITC (**1**) gave

1,4,5,6,7,8,9,10-octahydro-2,4,4-trimethyl-1-phenyl-1,5-benzodiazocine-6(1*H*)-thione (**108**) as the major product and 1-phenyl-4,4,6-trimethyl-3,4-dihydro-1*H*-pyrimidine-2-thione (**47**) as the minor product via the intermediate 2-phenylamino-cyclohex-1-enecarbothioic acid (1,1-dimethyl-3-oxo-butyl)-amide (**107**).[107] The condensation of ethyl-β-anilino crotonate (**109**) with DMO-ITC (**1**) gave an intermediate 3-[(3-isothiocyanato-1,3-dimethyl-but-1-enyl)-phenyl-amino]-but-2-enoic acid ethyl ester (**110**) which on elimination of ethyl acetoacetate gave 1-phenyl-4,4,6-trimethyl-3,4-dihydro-1*H*-pyrimidine-2-thione (**47**) and phenyl-(4,4,6-trimethyl-4*H*-[1,3]thiazin-2-yl)-amine (**48**)[108] (Scheme 20).

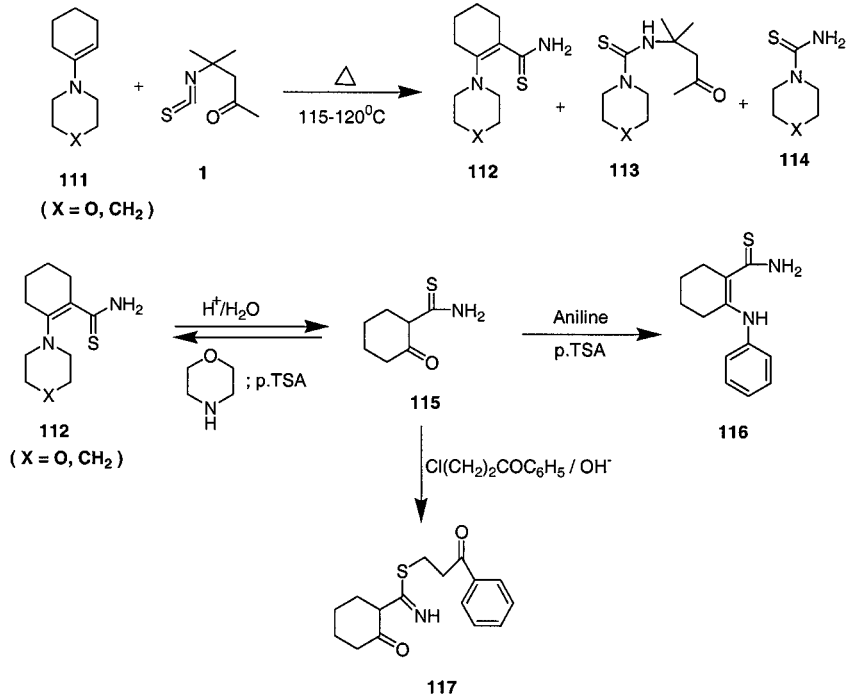


SCHEME 20

Heterocycles Having Tertiary Nitrogen Atom

At an ambient temperature, the condensation of *N*-(cyclohex-1-enyl)-morpholine (**111**) [X = O] and DMO-ITC (**1**) showed little progress but

on heating at 115–120°C under anhydrous condition for about 20 h gave three products (i.e., 2-morpholin-4-yl-cyclohex-1-enecarbothioic acid amide (**112**) [X = O] as the major and morpholine-4-carbothioic acid (1,1-dimethyl-3-oxo-butyl)-amide (113) [X = O] and morpholine-4-carbothioic acid amide (**114**) [X = O] as the minor products). Likewise, *N*-(cyclohex-1-enyl)-piperidine (**111**) [X = CH_2] gave the three products: 2-piperidin-1-yl-cyclohex-1-enecarbothioic acid amide (**112**) [X = CH_2], piperidine-1-carbothioic acid (1,1-dimethyl-3-oxo-butyl)-amide (**113**) [X = CH_2], and piperidine-1-carbothioic acid amide (**114**) [X = CH_2].[107] On acid hydrolysis both the compounds (**112**) [X = O] and [X = CH_2] formed the same product, 2-oxocyclohexanecarbothioic acid amide (**115**).[107] The compound (**115**) on reaction with morpholine and aniline in the presence of p-toluenesulphonic acid to furnished compounds (**112**) [X = O] and 2-phenylamino-cyclohex-2-enecarbothioic acid amide (**116**) respectively. On the other hand, in the presence of aq. sodium hydroxide, (**115**) reacts with β-chloropropiophenone to give 2-oxo-cyclohexane- carboximidothioic-acid-3-oxo-3-phenyl-propyl-ester (**117**)[109] (Scheme 21).

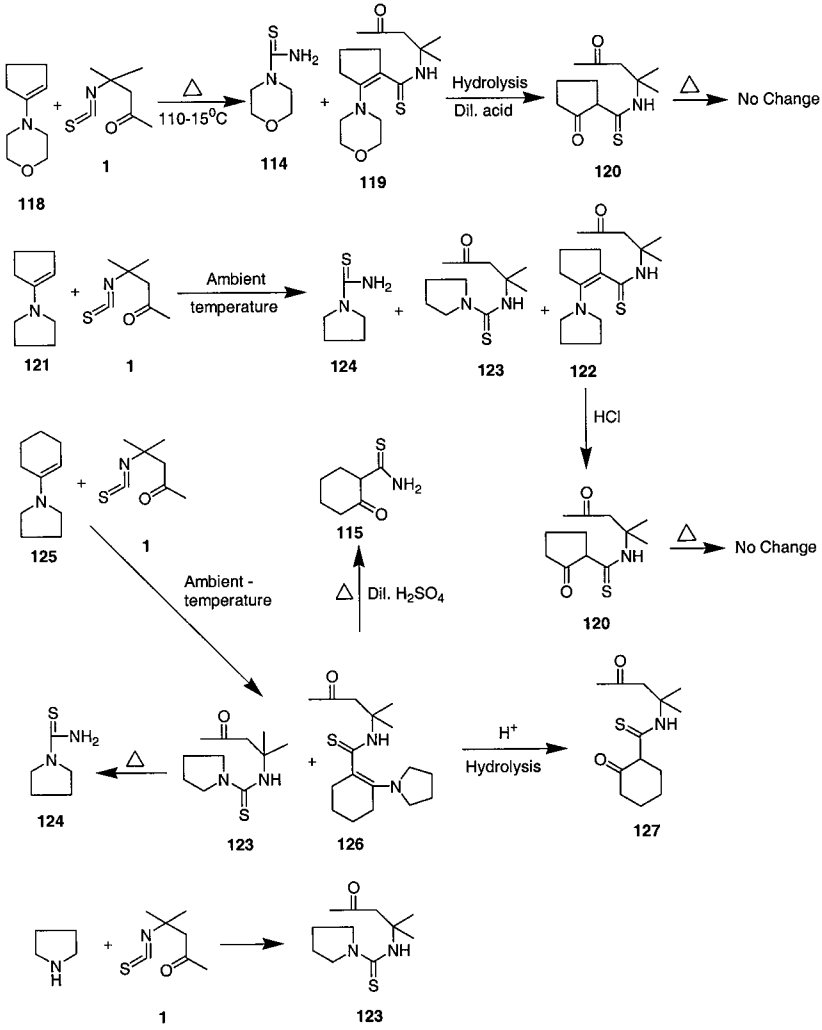


SCHEME 21

The reaction of *N*-(cyclopent-1-enyl)morpholine (**118**) with DMO-ITC (**1**) was performed at 110–115°C and gave 2-morpholin-4-yl-cyclopent-1-enecarbothioic acid (1,1-dimethyl-3-oxo-butyl)-amide (**119**) and morpholine-4-carbothioic acid amide (**114**). The product (**119**) on hydrolysis with dil. acid (HCl or H_2SO_4) gave 2-oxo-cyclopentane carbothioic acid (1,1-dimethyl-3-oxo-butyl)-amide (**120**) which on heating did not undergo any change. The condensation of cyclopent-1-enyl-pyrrolidine (**121**) and DMO-ITC (**1**) at ambient temperature furnished 2-pyrrolidin-1-yl-cyclopent-1-enecarbothioic acid(1,1-dimethyl-3-oxo-butyl)-amide (**122**), pyrrolidine-1-carbothioic acid(1,1-dimethyl-3-oxo-butyl)-amide (**123**), and pyrrolidine-1-carbothioic acid amide (**124**). The compound (**122**) was found to be hydrolyzed on heating with dil. HCl to (**120**) and was not changed further on heating. *N*-(Cyclohex-1-enyl)pyrrolidine (**125**) underwent condensation with DMO-ITC (**1**) at ambient temperature for 5 h and gave (**123**) and 2-pyrrolidin-1-yl-cyclohex-1-enecarbothioic acid(1,1-dimethyl-3-oxo-butyl)-amide (**126**). Compound (**123**) on heating, underwent β-elimination to form (**124**). Hydrolysis of compound (**126**) with dil. H_2SO_4 gave a mixture of products but the major was 2-oxo-cyclohexanecarbothioic acid(1,1-dimethyl-3-oxo-butyl)-amide (**127**). The compound (**126**) on heating followed by hydrolysis with dil. H_2SO_4 underwent β-elimination to form (**115**).[110,111] It is interesting to note that pyrrolidine itself underwent a vigorous reaction with DMO-ITC (**1**) and gave (**123**)[110] (Scheme 22).

Amino Alcohols

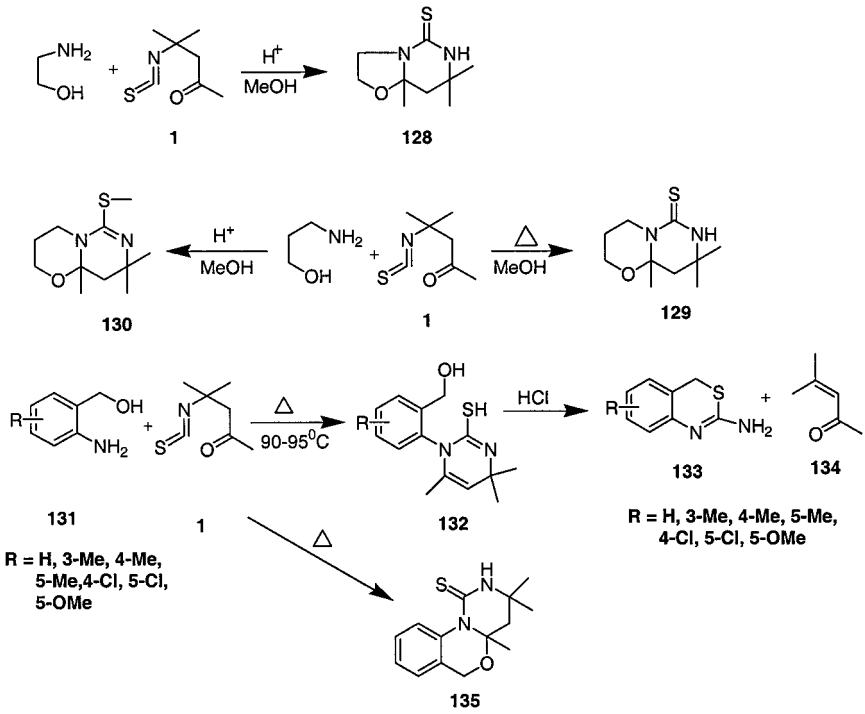
The condensation of 2-amino ethanol with DMO-ITC (**1**) at pH-2 gave 7,7,8a-trimethyl-hexahydro-oxazolo[3,2-*c*]pyrimidine-5-thione (**128**).[62,77,96] The reaction of DMO-ITC (**1**) with 3-aminopropanol at reflux temperature using methanol as a solvent gave 8,8,9a-trimethyl-hexahydro-pyrimido[6,1-*b*][1,3]oxazine-6-thione (**129**); however when the same reaction was done using 1.1 mmol equivalent of sulfuric acid, the product was found to be 8, 8, 9a-trimethyl-6-methylsulfanyl-3,4,9,9a-tetrahydro-2*H*,8*H*-pyrimido[6,1-*b*][1,3]oxazine (**130**).[61,96] When *o*-aminobenzyl alcohol or its derivatives (**131**) were heated with DMO-ITC (**1**) at 90–95°C it gave the respective [2-(2-mercapto-4,4,6-trimethyl-4*H*-pyrimidin-1-yl)-phenyl]-methanols (**132**), which, on the treatment with HCl, gave 4*H*-benzo[*d*][1,3]thiazin-2-ylamine (**133**) and 4-methyl-pent-3-en-2-one (**134**).[112] On the other hand *o*-aminobenzyl alcohol condensed with DMO-ITC (**1**) at the reflux temperature of xylene gave 2,2,10a-trimethyl-1,2,3,10a-tetrahydro-9*H*-10-oxa-3,4a-diaza-phenanthrene-4-thione (**135**)[96] (Scheme 23).



SCHEME 22

Amino Phenols

Condensation of *o*, *m*, or *p*-amino phenols with DMO-ITC (**1**) gave their respective 2,3 or 4-(2-mercapto-4,4,6-trimethyl-4*H*-pyrimidin-1-yl)-phenols (**136**) in the presence of an acid, which on heating with conc. HCl, were rearranged to their respective 2, 3, or 4-(4,4,6-trimethyl-4*H*-[1,3]thiazin-2-ylamino)-phenols (**137**).[98] 4-(2-mercapto-4,4,6-trimethyl-4*H*-pyrimidin-1-yl)-phenol (**136**) also was obtained when an aqueous

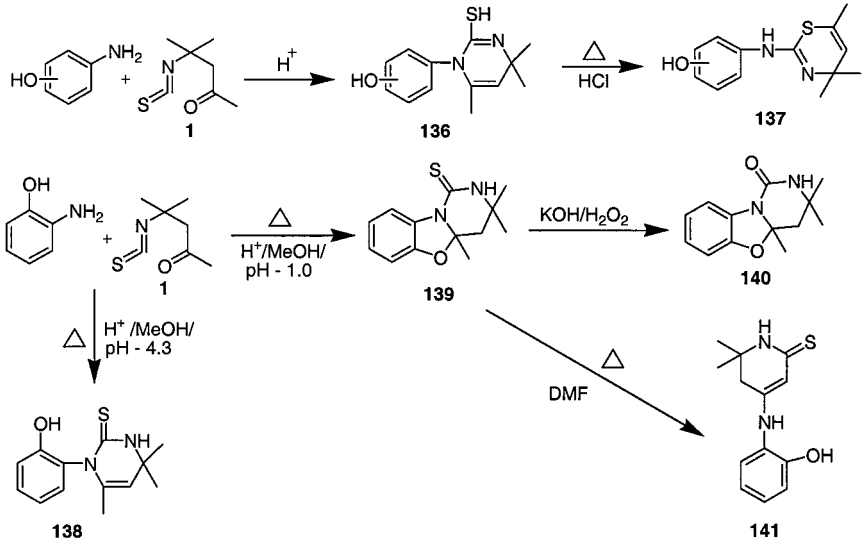


SCHEME 23

solution of *p*-amino phenol was refluxed with DMO-ITC (**1**) in the presence of HCl.[68] The reaction of *o*-amino phenol with DMO-ITC (**1**) at pH = 4.3 gave 1-(2-hydroxy-phenyl)-4,4,6-trimethyl-3,4-dihydro-1*H*-pyrimidine-2-thione (**138**).[62] However, when the same reaction was done at pH = 1.0, it gave 2,2,9a-trimethyl-1,2,3,9a-tetrahydro-9-oxa-3,4a-diaza-fluorene-4-thione (**139**),[62,96] which on the treatment with H_2O_2/KOH was converted into 2,2,9a-trimethyl-1,2,3,9a-tetrahydro-9-oxa-3,4a-diaza-fluorene-4-one (**140**).[96] On the other hand, the methyl pyrimidine-pyridine rearrangement took place when (**139**) was heated with DMF and gave 4-(2-hydroxy-phenylamino)-6,6-dimethyl-5,6-dihydro-1*H*-pyridine-2-thione (**141**)[96] (Scheme 24).

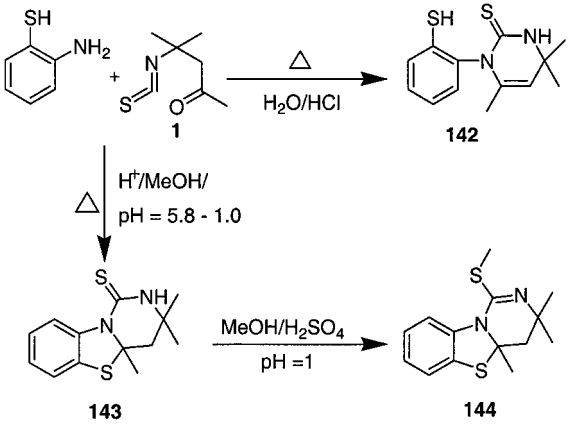
Amino Thiophenols

When aqueous solution of *o*-amino thiophenol was refluxed with DMO-ITC (**1**) in the presence of an acid it gave 1-(2-mercapto-phenyl)-4,4,6-trimethyl-3,4-dihydro-1*H*-pyrimidine-2-thione (**142**),[68] but when



SCHEME 24

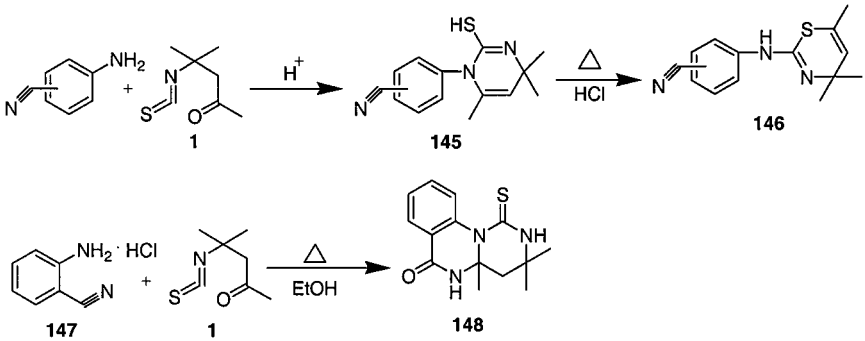
the same reaction was done in MeOH under different pH conditions it gave condensed heterocycle 2,2,9a-trimethyl-1,2,3,9a-tetrahydro-9-thia-3,4a-diaza-fluorene-4-thione (**143**),[62,96] which on refluxing in $MeOH/H_2SO_4$ (pH = 1) gave S-methylated product, 2,2,9a-trimethyl-4-methylsulfanyl-1,9a-dihydro-2*H*-9-thia-3,4a-diaza-fluorene (**144**)[57] (Scheme 25).



SCHEME 25

Amino Benzonitriles

Condensation of *o*, *m*, or *p*-amino benzonitriles with DMO-ITC (**1**) gave their respective 2, 3, or 4-(2-mercapto-4,4,6-trimethyl-4*H*-pyrimidin-1-yl)-benzonitriles (**145**) in the presence of an acid which on heating with conc. HCl was rearranged to their respective 2, 3, or 4-(4,4,6-trimethyl-4*H*-[1,3]thiazin-2-ylamino)-benzonitriles (**146**).[98] On the other hand, when *o*-amino benzonitrile hydrochloride (**147**) was refluxed with DMO-ITC (**1**) in ethyl alcohol it gave 2,2,10a-trimethyl-4-thioxo-1,2,3,4,10,10a-hexahydro-3,4a,10-triaza-phenanthren-9-one (**148**)[113] (Scheme 26).

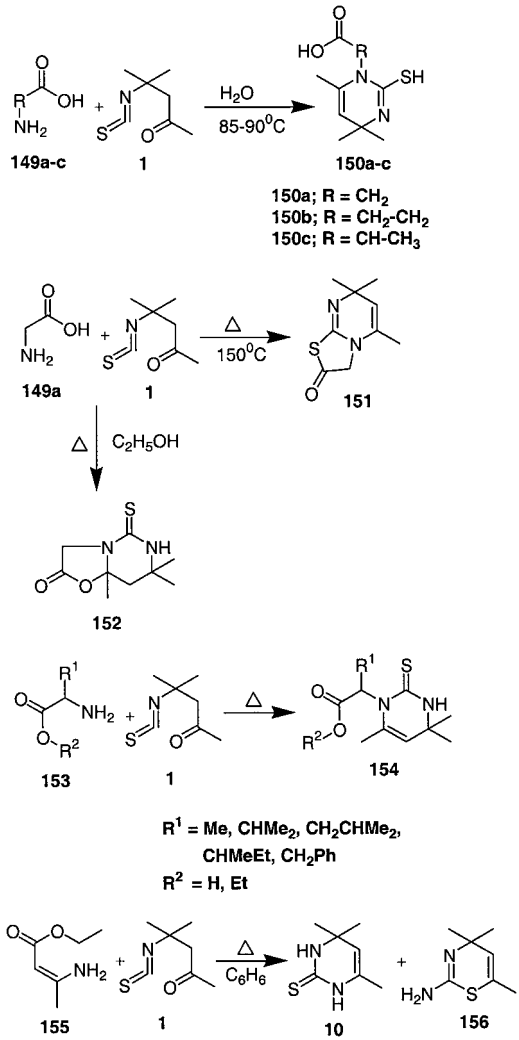


SCHEME 26

Amino Acids or Their Derivatives

Amino acids having a primary amino group (e.g., glycine (**149a**; R = CH_2), β-alanine (**149b**; R = CH_2—CH_2) and *dl*-α-alanine (**149c**; R = CH—CH_3)) when heated with DMO-ITC (**1**) in the presence of water gave respective pyrimidinethiol (**150a–c**), having an acid substituent at position-1. The product (**150a–c**) were assigned as: (2-mercapto-4,4,6-trimethyl-4*H*-pyrimidin-1-yl)-acetic acid (**150a**; from glycine), 3-(2-mercapto-4,4,6-trimethyl-4*H*-pyrimidin-1-yl)-propionic acid (**150b**; from β-alanine), and 2-(2-mercapto-4,4,6-trimethyl-4*H*-pyrimidin-1-yl)-propionic acid (**150c**; from *dl*-α-alanine) respectively.[114] The reaction of DMO-ITC (**1**) with glycine without solvent and at 150°C gave 5,7,7-trimethyl-7*H*-thiazolo[3,2*a*]pyrimidin-2-one (**151**),[95] whereas by using ethyl alcohol or hexanol as a solvent and on refluxing gave 7,7,8a-trimethyl-5-thioxo-tetrahydro-oxazolo[3,2-*c*]pyrimidin-2-one (**152**).[115,116] α-(4,4,6-Trimethyl-2-thioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-carboxylic acids or esters (**154**)[117] were prepared

by heating DMO-ITC (**1**) with α-amino acids or esters (**153**). Ethyl-β-aminocrotonate (**155**) on condensation with DMO-ITC (**1**) in hexane, benzene, or toluene formed 4,4,6-trimethyl-3,4-dihydro-1*H*-pyrimidine-2-thione (**10**) as the major product and 4,4,6-trimethyl-4*H*- [1,3]thiazin-2-ylamine (**156**) as the minor component. The use of ether, acetonitrile, butan-2-one, ethyl acetate, chloroform as solvents reversed the product ratio[118,119] (Scheme 27).

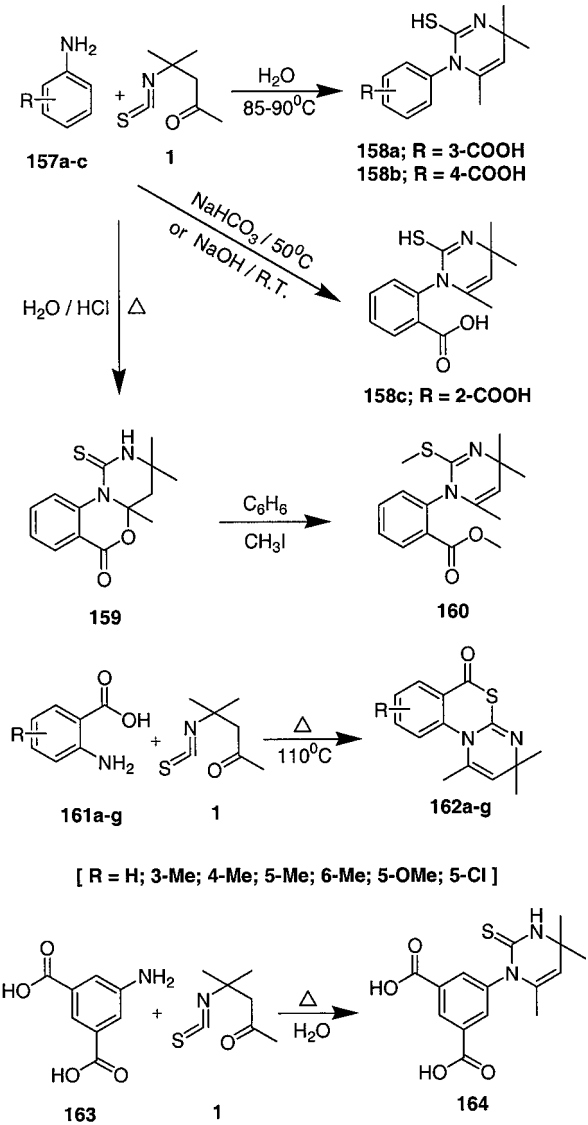


SCHEME 27

Condensation of *m* or *p*-amino benzoic acids (**157a**,**b**) with DMO-ITC (**1**) gave their respective 3 or 4-(2-mercapto-4,4,6-trimethyl-4*H*-pyrimidin-1-yl)-benzoic acids (**158a**,**b**).[78,114] In the case of *o*-amino benzoic acid (**157c**), the condensed product 2-(2-mercapto-4,4,6-trimethyl-4*H*-pyrimidin-1-yl)-benzoic acid (**158c**) was obtained only when the reaction was done either in $NaHCO_3$ or NaOH solution.[120] But when *o*-amino benzoic acid (**157c**) was refluxed with DMO-ITC (**1**) in the presence of an acid (HCl) and H_2O, the product was found to be 2,2,10a-trimethyl-4-thioxo-1,3,4,10a-tetrahydro-2*H*-10-oxa-3,4a-diaza-phenanthren-9-one (**159**)[103,113,115,116] which on methylation was converted into 2-(4,4,6-trimethyl-2-methylsulfanyl-4*H*-pyrimidin-1-yl)-benzoic acid methyl ester (**160**) with simultaneous esterification of the carboxy group under the phase-transfer condition.[103] An equimolar mixture of *o*-amino benzoic acid or its substituted derivatives (**161a–g**) when heated with DMO-ITC (**1**) gave the corresponding condensed products: 2,2,4-trimethyl-2*H*-10-thia-1,4a-diaza-phenanthren-9-one (**162a**), 2,2,4,5-tetramethyl-2*H*-10-thia-1,4a-diaza-phenanthren-9-one (**162b**), 2,2,4,6-tetramethyl-2*H*-10-thia-1,4a-diaza-phenanthren-9-one (**162c**), 2,2,4,7-tetramethyl-2*H*-10-thia-1,4a-diaza-phenanthren-9-one (**162d**), 2,2,4,8-tetramethyl-2*H*-10-thia-1,4a-diaza-phenanthren-9-one (**162e**), 7-methoxy-2,2,4-trimethyl-2*H*-10-thia-1,4a-diaza-phenanthren-9-one (**162f**), and 7-chloro-2,2,4-trimethyl-2*H*-10-thia-1,4a-diaza-phenanthren-9-one (**162g**).[112,120] The condensation of amino isophthalic acid (**163**) with DMO-ITC (**1**) in the presence of H_2O gave 5-(4,4,6-trimethyl-2-thioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-isophthalic acid (**164**)[78] (Scheme 28).

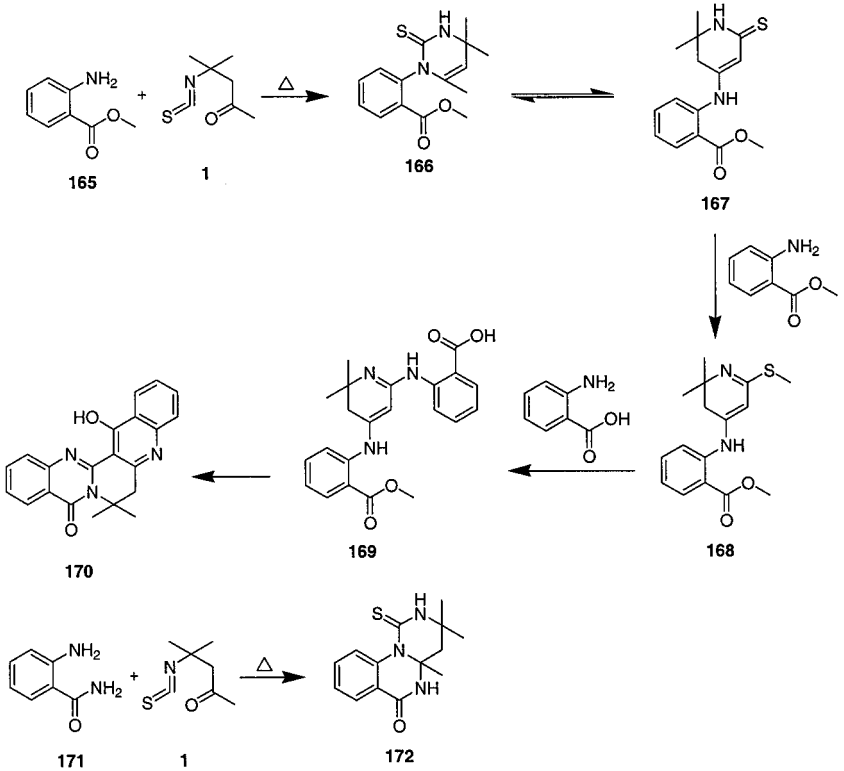
The reaction of DMO-ITC (**1**) with methyl anthranilate (**165**) takes place via 2-(4,4,6-trimethyl-2-thioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-benzoic acid methyl ester (**166**), which was rearranged to 2-(2,2-dimethyl-6-thioxo-1,2,3,6-tetrahydro-pyridin-4-ylamino)-benzoic acid methyl ester (**167**). (**167**) was alkylated by methyl anthranilate to the corresponding 2-(2,2-dimethyl-6-methylsulfanyl-2,3-dihydro-pyridin-4-ylamino)-benzoic acid methyl ester (**168**) which reacts with anthranilic acid via (**169**) to the 14-hydroxy- 7,7-dimethyl-6,7-dihydro-5,7a,13-triaza-pentaphen-8-one (**170**).[113,121] Anthranilamide (**171**) when treated with DMO-ITC (**1**) gave the condensed product 2,2,10a-trimethyl-4-thioxo-1,2,3,4,10,10a-hexahydro-3,4a,10-triaza-phenanthren-9-one (**172**)[116] (Scheme 29).

When a mixture of 3-amino-2-naphthoic acid (**173**) and DMO-ITC (**1**) was heated at 115–120°C it gave 1,3,3-trimethyl-3*H*-5-thia-4,12b-diaza-benzo[*a*]anthracen-6-one (**174**).[122] During the condensation of 6-amino-benzo[1,3]dioxole-5-carboxylic acid methyl ester (**175**) with DMO-ITC



SCHEME 28

(**1**) at 100°C gave 6-(4,4,6-trimethyl-2-thioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-benzo[1,3]dioxole-5-carboxylic acid methyl ester (**176**) which on the treatment with sodium ethoxide gave 1,3,3-trimethyl-3*H*-8,10-dioxa-5-thia-4,11b-diaza-cyclopenta[*b*]phenanthren-6-one (**177**).[123] The condensation of 2-amino-4,5-dimethyl-thiophene-3-carboxylic acid

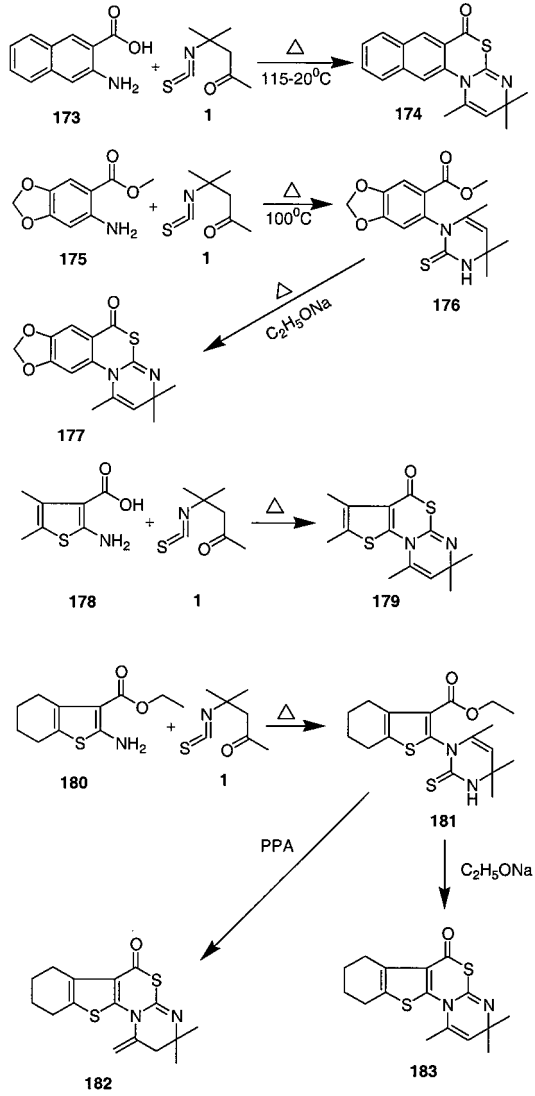


SCHEME 29

(**178**) with DMO-ITC (**1**) gave 2,3,7,7,9-pentamethyl-7*H*-1,5-dithia-6,9a-diaza-cyclopenta[*a*]naphthalen-4-one (**179**).[124] Codensation of 2-amino-4,5,6,7-tetrahydro-benzo[*b*]thiophene-3-carboxylic acid ethyl ester (**180**) with DMO-ITC (**1**) gave 2-(4,4,6-trimethyl-2-thioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-4,5,6,7-tetrahydro-benzo[*b*]thiophene-3-carboxylic acid ethyl ester (**181**), cyclization of which with polyphosphoric acid (PPA) gave 3,3-dimethyl-1-methylene-2,3,7,8,9,10-hexahydro-1*H*-5,11-dithia-4,11b-diaza-benzo[*a*]fluoren-6-one (**182**). Cyclization of (**181**) with C_2H_5ONa gave 1,3,3-trimethyl-7,8,9,10-tetrahydro-3*H*-5,11-dithia-4,11b-diaza-benzo[*a*]fluoren-6-one (**183**)[125] (Scheme 30).

Hydrazines

When an aqueous cold solution of hydrazine hydrate was reacted with DMO-ITC (**1**) in the presence of water and HCl it gave 1-amino-6-hydroxy-4,4,6-trimethyl-tetrahydro-pyrimidine-2-thione (**184**) which

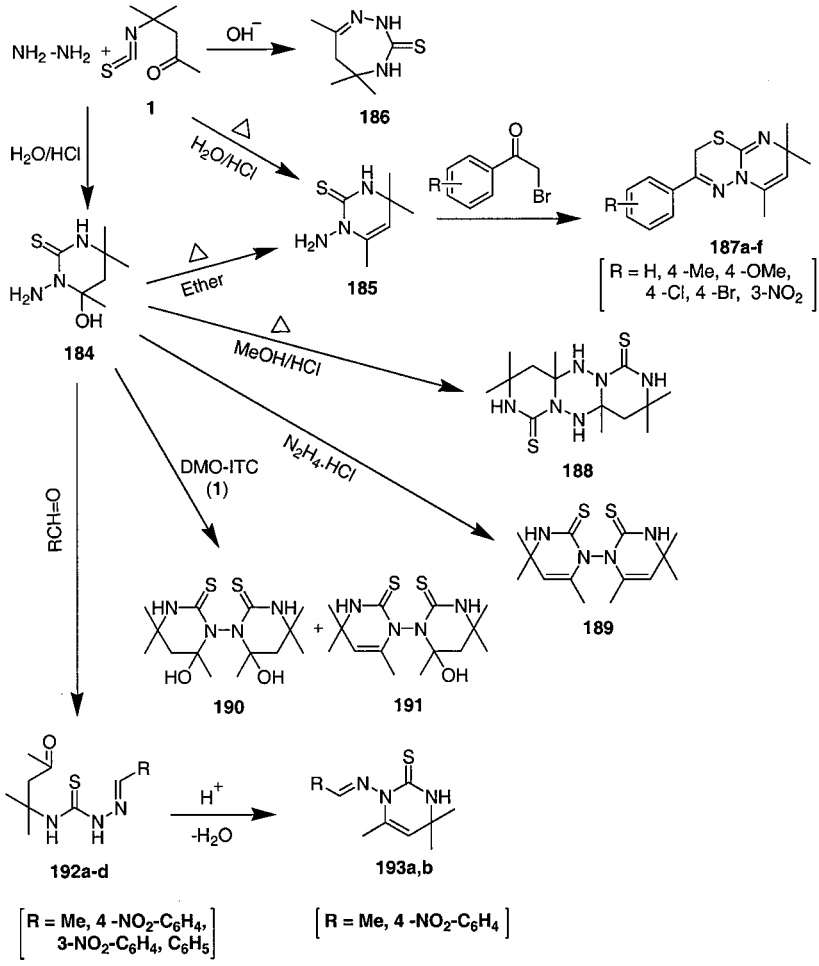


SCHEME 30

gets converted into 1-amino-4,4,6-trimethyl-3,4-dihydro-1*H*-pyrimidine-2-thione (**185**) when heated with trimethylsilylchloride in ether.[126] 1-Amino-4,4,6-trimethyl-3,4-dihydro-1*H*-pyrimidine-2-thione (**185**) also was obtained when the mixture of water, DMO-ITC (**1**), and H_2SO_4 or HCl was treated with hydrazine hydrate, dissolved in water, and raised to the temperature of 80°C.[68,78,127] On the other hand,

when hydrazine hydrate reacts with DMO-ITC (**1**) in alkaline solution it gave 5,5,7-trimethyl-2,4,5,6-tetrahydro-[1,2,4]triazepine-3-thione (**186**).[128,129] 1-Amino-4,4,6-trimethyl-3,4-dihydro-1*H*-pyrimidine-2-thione (**185**) when refluxed in ethanol with α-bromo-acetophenone or its derivatives (e.g., 2-bromo-1-(4-Me or 4-OMe or 4-Cl or 4-Br or 3-NO_2-phenyl)-ethanones) gave corresponding 6,8,8-trimethyl-3-phenyl-2*H*,8*H*-pyrimido[2,1-*b*][1,3,4]thiadiazine (**187a**) or 3-(4-methyl or 4-methoxy or 4-chloro or 4-bromo or 3-nitro-phenyl)-6,8,8-trimethyl-2*H*,8*H*-pyrimido[2,1-*b*][1,3,4]thiadiazine (**187b–f**).[127] The product (**184**) when refluxed with methanol in the presence of HCl gave 3,3,4a,7,7,8a-hexamethyl-octahydro-2,6,9,9a,10,10a-hexaaza-anthracene-1,5-dithione (**188**),[126] whereas on cyclocondensation with N_2H_4.HCl gave 4,4,6,4′,4′,6′-hexamethyl-3,4,3′,4′-tetrahydro-[1,1′]bipyrimidinyl-2,2′-dithione (**189**). Cyclocondensation of (**184**) with DMO-ITC (**1**) gave 6,6′-dihydroxy-4,4,6,4′,4′,6′-hexamethyl-octahydro-[1,1′] bipyrimidinyl-2,2′-dithione (**190**) and 6-hydroxy-4,4,6,4′,4′,6′-hexamethyl-3,4,5,6,3′,4′-hexahydro-[1,1′]bipyrimidinyl-2,2′-dithione (191) in 81% and 8% respectively. Dehydration of (**190**) or (**191**) by refluxing in alcohol with HCl gave 4,4,6,4′,4′,6′-hexamethyl-3,4,3′,4′-tetrahydro-[1,1′]bipyrimidinyl-2,2′-dithione (**189**).[130] On the other hand, the reaction of (**184**) with ordinary aldehydes gave respective (**192a–d**). The compounds (**192a**,**b**) were found to be converted into 1-ethylideneamino-4,4,6-trimethyl-3,4-dihydro-1*H*-pyrimidine-2-thione (**193a**) and 1-(benzylidene-amino)-4,4,6-trimethyl-3,4-dihydro-1*H*-pyrimidine-2-thione (**193b**), respectively, in an acidic medium[131] (Scheme 31).

The reaction of hydrazine derivatives (**194a–f**) with DMO-ITC (**1**) in alkaline solution gave respective 5,5,7-trimethyl-2,4,5,6-tetrahydro-[1,2,4]triazepine-3-thione (**195a**), 2,5,5,7-tetramethyl-2,4,5,6-tetrahydro-[1,2,4]triazepine-3-thione (**195b**), 2-ethyl-5,5,7-trimethyl-2,4,5,6-tetrahydro-[1,2,4]triazepine-3-thione (**195c**), 2-cyclohexyl-5,5,7-trimethyl-2,4,5,6-tetrahydro-[1,2,4]triazepine-3-thione (**195d**), 5,5,7-trimethyl-2-phenethyl-2,4,5,6-tetrahydro-[1,2,4]triazepine-3-thione (**195e**), and 2-(2-hydroxy-ethyl)-5,5,7-trimethyl-2,4,5,6-tetrahydro-[1,2,4]triazepine-3-thione (**195f**). Alkylation of (**195a**,**b**) with methyl iodide gave their S-methylated derivatives 5,5,7-trimethyl-3-methylsulfanyl-5,6-dihydro-2*H*-[1,2,4]triazepine (**196a**) and 2,5,5,7-tetramethyl-3-methylsulfanyl-5,6-dihydro-2*H*-[1,2,4]triazepine (**196b**) respectively. Similarly, the alkylation of (**195b,d**) with bromo-acetic acid ethyl ester gave their S-substituted derivatives (2,5,5,7-tetramethyl-5,6-dihydro-2*H*-[1,2,4]triazepin-3-ylsulfanyl)-acetic acid ethyl ester (**197b**) and (2-cyclohexyl-5,5,7-trimethyl-5,6-dihydro-2*H*-[1,2,4]triazepin-3-ylsulfanyl)-acetic acid ethyl ester (**197d**),

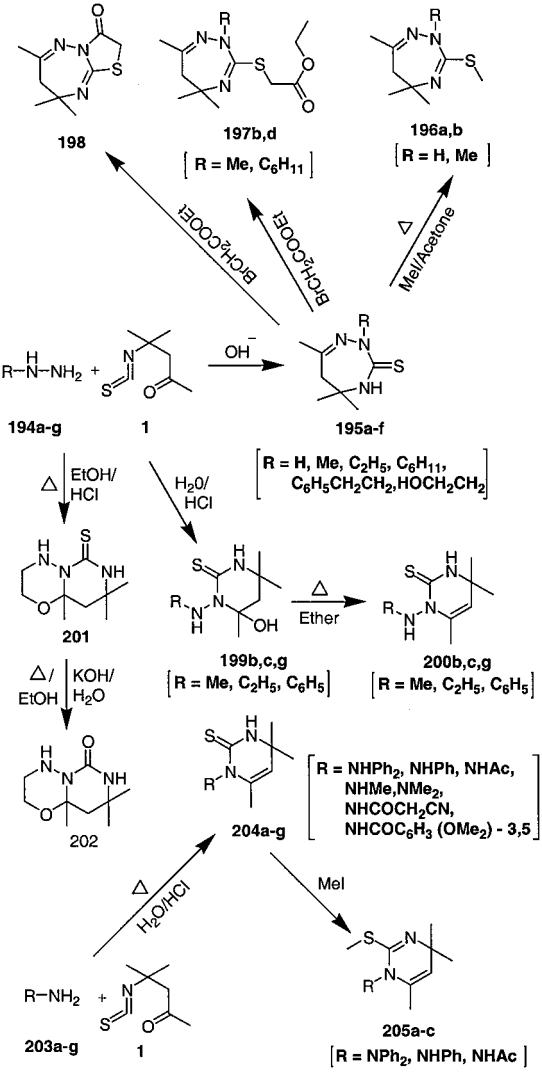


SCHEME 31

respectively, but in the case of (**195a**), the fused ring product 6,8,8-trimethyl-7,8-dihydro-thiazolo[3,2-b][1,2,4]triazepin-3-one (**198**) was obtained.[128] On the other hand, the reaction of hydrazine derivatives (**194b**,**c**,**g**) with DMO-ITC (**1**) at low temperature and in the presence of water and HCl gave 6-hydroxy-4,4,6-trimethyl-1-methylamino-tetrahydro-pyrimidine-2-thione (**199b**), 1-ethylamino-6-hydroxy-4,4,6-trimethyl-tetrahydro-pyrimidine-2-thione (**199c**), and 1-anilino-6-hydroxy-4,4,6-trimethyl-tetrahydro-pyrimidine-2-thione (**199g**) respectively. The products (**199b**,**c**,**g**) were easily converted into 4,4,6-trimethyl-1-methylamino-3,4-dihydro-1*H*-pyrimidine-2-thione (**200b**),

1-ethylamino-4,4,6-trimethyl-3,4-dihydro-1*H*-pyrimidine-2-thione (**200c**), and 1-anilino-4,4,6-trimethyl-3,4-dihydro-1*H*-pyrimidine-2-thione (**200g**), respectively, when heated with trimethylsilyl chloride in ether. But when hydrazine derivative, 2-hydrazino-ethanol (**194f**) was refluxed with DMO-ITC (**1**) and ethanol in the presence of HCl, it gave condensed product 8,8,9a-trimethyl-hexahydro-pyrimido[6,1-*b*][1,3,4]oxadiazine-6-thione (**201**) which was desulfurized when heated with ethyl alcohol and H_2O_2 in the presence of KOH and gave 8,8,9a-trimethyl-hexahydro-pyrimido[6,1-*b*][1,3,4]oxadiazin-6-one (**202**).[126] On warming the mixture of substituted hydrazines (**203a–g**), water, HCl, and DMO-ITC (**1**) in a water bath, the products 1-diphenylamino-4,4,6-trimethyl-3,4-dihydro-1*H*-pyrimidine-2-thione (**204a**), 4,4,6-trimethyl-1-phenylamino-3,4-dihydro-1*H*-pyrimidine-2-thione (**204b**), *N*-(4,4,6-trimethyl-2-thioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-acetamide (**204c**), 4,4,6-trimethyl-1-methylamino-3,4-dihydro-1*H*-pyrimidine-2-thione (**204d**), 1-dimethylamino-4,4,6-trimethyl-3,4-dihydro-1*H*-pyrimidine-2-thione (**204e**), 2-cyano-*N*-(4,4,6-trimethyl-2-thioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-acetamide (**204f**), and 3,5-dimethoxy-*N*-(4,4,6-trimethyl-2-thioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-benzamide (**204g**) were obtained respectively. Methylation of (**204a–c**) with methyl iodide gave S-methylated derivatives, diphenyl-(4,4,6-trimethyl-2-methylsulfanyl-4*H*-pyrimidin-1-yl)-amine (**205a**), phenyl-(4,4,6-trimethyl-2-methylsulfanyl-4*H*-pyrimidin-1-yl)-amine (**205b**), and *N*-(4,4,6-trimethyl-2-methylsulfanyl-4*H*-pyrimidin-1-yl)-acetamide (**205c**) respectively[132] (Scheme 32).

Condensation of hydrazine derivatives (**206a**,**b**) with DMO-ITC (**1**) gave condensed products (4,4,6-trimethyl-2-thioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-thiourea (**207a**) and 1-methyl-1-(4,4,6-trimethyl-2-thioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-thiourea (**207b**) respectively.[133] Similarly, the condensation of acid hydrazides (**208a–k**) with DMO-ITC (**1**) gave *N*-(4,4,6-trimethyl-2-thioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-acetamide (**209a**), *N*-(4,4,6-trimethyl-2-thioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-propionamide (**209b**), *N*-(4,4,6-trimethyl-2-thioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-butyramide (**209c**), *N*-(4,4,6-trimethyl-2-thioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-benzamide (**209d**), 2-phenyl-*N*-(4,4,6-trimethyl-2-thioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-acetamide (**209e**), 4-nitro-*N*-(4,4,6-trimethyl-2-thioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-benzamide (**209f**), 4-chloro-*N*-(4,4,6-trimethyl-2-thioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-benzamide (**209g**), 4-hydroxy-*N*-(4,4,6-trimethyl-2-thioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-benzamide (**209h**), 4-methoxy-*N*-(4,4,6-trimethyl-2-thioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-benzamide (**209i**), 2-phenoxy-*N*-(4,4,6-trimethyl-2-thioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-acetamide (**209j**), and



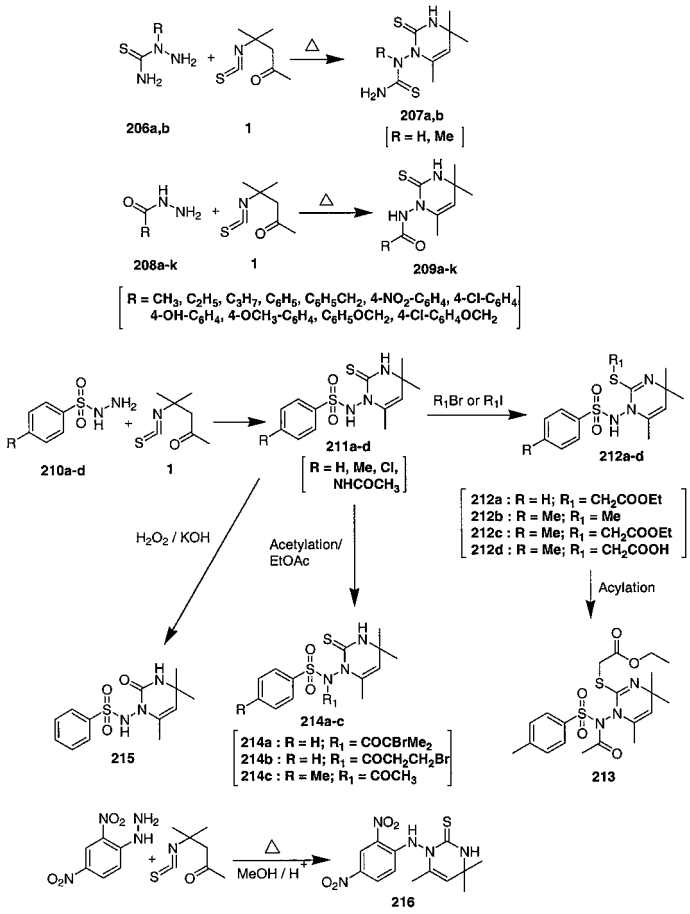
SCHEME 32

2-(4-chloro-phenoxy)-*N*-(4,4,6-trimethyl-2-thioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-acetamide (**209k**) respectively.[134] DMO-ITC (**1**) when treated with phenyl sulfonyl hydrazides (**210a–d**) gave the condensed products *N*-(4,4,6-trimethyl-2-thioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-benzenesulfonamide (**211a**), 4-methyl-*N*-(4,4,6-trimethyl-2-thioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-benzenesulfonamide (**211b**),

4-chloro-*N*-(4,4,6-trimethyl-2-thioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-benzenesulfonamide (**211c**), and *N*-[4-(4,4,6-trimethyl-2-thioxo-3,4-dihydro-2*H*-pyrimidin-1-ylsulfamoyl)-phenyl]acetamide (**211d**) respectively.[135,136] Alkylation of (**211a**) with bromo or iodo–acetic acid ethyl ester gave (1-benzenesulfonylamino-4,4,6-trimethyl-1,4-dihydro-pyrimidin-2-yl-sulfanyl)-acetic acid ethyl ester (**212a**). Similarly, the alkylation of (**211b**) with methyl iodide or bromide; bromo or iodo-acetic acid ethyl ester and bromo or iodo-acetic acid gave *S*-alkylated derivatives 4-methyl-*N*-(4,4,6-trimethyl-2-methylsulfanyl-4*H*-pyrimidin-1-yl)-benzenesulfonamide (**212b**), [4,4,6-trimethyl-1-(toluene-4-sulfonylamino)-1,4-dihydro-pyrimidin-2-ylsulfanyl]-acetic acid ethyl ester (**212c**), and [4,4,6-trimethyl-1-(toluene-4-sulfonylamino)-1,4-dihydro-pyrimidin-2-ylsulfanyl]-acetic acid (**212d**) respectively. Acylation of (**212c**) gave {1-[acetyl-(toluene-4-sulfonyl)-amino]-4,4,6-trimethyl-1,4-dihydro-pyrimidin-2-ylsulfanyl}-acetic acid ethyl ester (**213**). When (**211a**,**b**) were acylated in ethyl acetate they gave their respective *N*-acylated derivatives *N*-(2-bromo-2-methyl-propionyl)-*N*-(4,4,6-trimethyl-2-thioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-benzene sulfonamide (**214a**), *N*-(3-bromo-propionyl)-*N*-(4,4,6-trimethyl-2-thioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-benzenesulfonamide (**214b**), and *N*-acetyl-4-methyl-*N*-(4,4,6-trimethyl-2-thioxo-3,4-dihydro-2*H*-pyrimidin-1-yl) benzenesulfonamide (**214c**). *N*-(4,4,6-Trimethyl-2-thioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-benzenesulfonamide (**211a**) was desulfurized when treated with H_2O_2 in the presence of KOH and gave *N*-(4,4,6-trimethyl-2-oxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-benzenesulfonamide (**215**).[136] The condensation of 2,4-dinitrophenyl hydrazine with DMO-ITC (**1**) in the presence of an acid as a catalyst, gave 1-(2,4-dinitro-phenylamino)-4,4,6-trimethyl-3,4-dihydro-1*H*-pyrimidine-2-thione (**216**)[60,97] (Scheme 33).

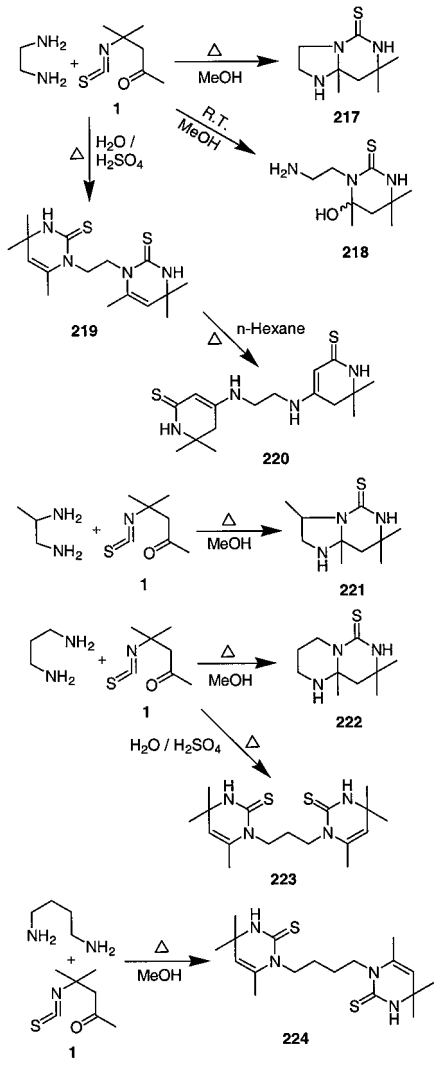
Aliphatic Diamines

When ethylenediamine was treated with DMO-ITC (**1**) under reflux temperature in methanol at pH = 9 gave 7,7,8a-trimethyl-hexahydro-imidazo[1,2-*c*]pyrimidine-5-thione (**217**),[61,96] but when the same reaction was carried out at room temperature, a complex mixture was obtained which on chromatographic separation gave only a minor product (i.e., 1-(2-amino-ethyl)-6-hydroxy-4,4,6-trimethyl-tetrahydro-pyrimidine-2-thione) (**218**).[61] On the other hand, two molar equivalent of DMO-ITC (**1**) treated with ethylenediamine at 85°C in the presence of water and H_2SO_4 gave 1,1′-ethylene-bis [4,4,6-trimethyl-3,4-dihydro-1*H*-pyrimidine-2-thione] (**219**)[77,96]



SCHEME 33

which were converted into 4,4′-ethyldiamino-bis[6,6-dimethyl-5,6-dihydro-1*H*-pyridine-2-thione] (**220**) when refluxed with n-hexane.[96] 1,2-Diaminopropane on condensation with DMO-ITC (**1**) at pH = 5 and reflux temperature in methanol gave 3,7,7,8a-tetramethyl-hexahydro-imidazo[1,2-*c*]pyrimidine-5-thione (**221**) in good yield.[61] Similarly, 1,3-diaminopropane gave 8,8,9a-trimethyl-octahydro-pyrimido[1,6-*a*]pyrimidine-6-thione (**222**), but when it was treated with two molar equivalent of DMO-ITC (**1**) gave 1,1′-propane-bis [4,4,6-trimethyl-3,4-dihydro-1*H*-pyrimidine-2-thione] (**223**).[96] DMO-ITC (**1**) reacts smoothly with 1,4-diaminobutane on refluxing in methanol at pH = 5 gave 1,1′-butane-bis [4,4,6-trimethyl-3,4-dihydro-1*H*-pyrimidine-2-thione] (**224**)[59] (Scheme 34).



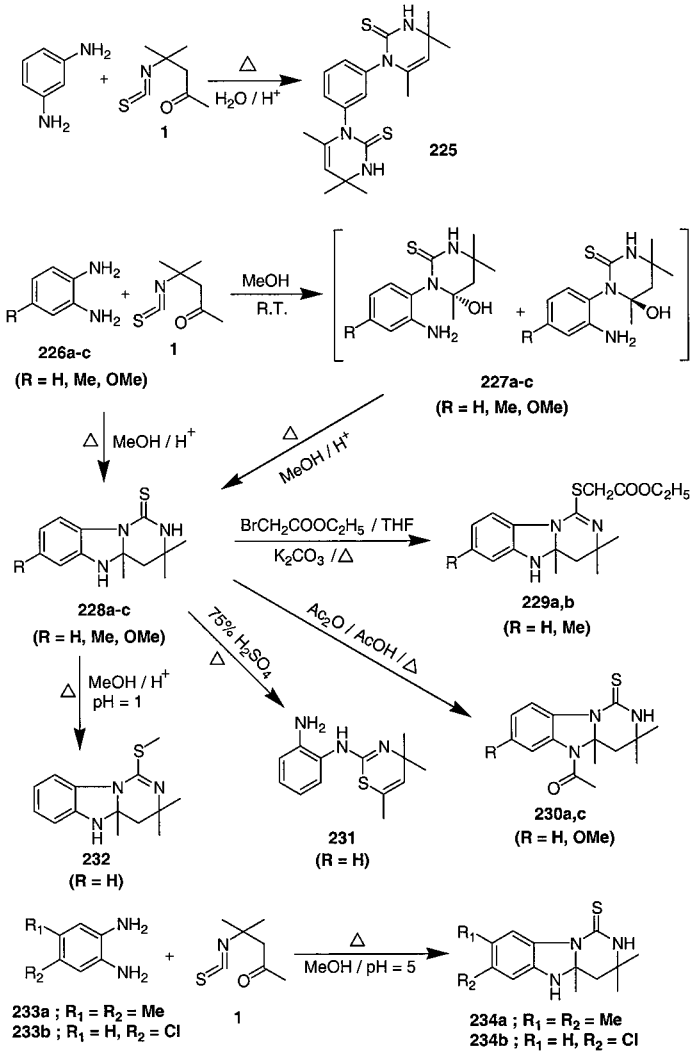
SCHEME 34

Aromatic Diamines

The reaction of *m*-phenylenediamine with two molar equivalent of DMO-ITC (**1**) at 85°C in the presence of water and H_2SO_4 gave a dimer 1,3-phenylene-bis [4,4,6-trimethyl-3,4-dihydro-1*H*-pyrimidine-2-thione] (**225**).[77] *o*-Phenylenediamine (**226a**), 4-methyl-1,2-phenylenediamine (**226b**), and 4-methoxy-1,2-phenylenediamine (**226c**) reacted with DMO-ITC (**1**) in MeOH at room temperature

gave respective isomeric mixtures of 1-(2-amino-phenyl)-6-hydroxy-4,4,6-trimethyl-tetrahydro-pyrimidine-2-thione (**227a**), 1-(2-amino-4-methyl-phenyl)-6-hydroxy-4,4,6-trimethyl-tetrahydro-pyrimidine-2-thione (**227b**), and 1-(2-amino-4-methoxy-phenyl)-6-hydroxy-4,4,6-trimethyl-tetrahydro-pyrimidine-2-thione (**227c**), respectively, which on refluxing with catalytic amount of sulfuric acid were cyclized to 3,3,4a-trimethyl-3,4,4a,5-tetrahydro-2*H*-benzo[4,5]imidazo[1,2-*c*]pyrimidine-1-thione (**228a**), 3,3,4a,7-tetramethyl-3,4,4a,5-tetrahydro-2*H*-benzo[4,5]imidazo[1,2-*c*]pyrimidine-1-thione (**228b**), and 7-methoxy-3,3,4a-trimethyl-3,4,4a,5-tetrahydro-2*H*-benzo[4,5]imidazo[1,2-*c*]pyrimidine-1-thione (**228c**) respectively.[137,62] The same products (**228a–c**) also were obtained by the direct condensation of DMO-ITC (**1**) with (**226a–c**), respectively,[62,96,137] in the presence of MeOH and catalytic amount of an acid. Pyrimidobenzimidazoles (**228a**,**b**) on refluxing with ethyl bromoacetate in the presence of potassium carbonate using tetrahydrofuran (THF) as solvent gave S-alkylated products (3,3,4a-trimethyl-3,4,4a,5-tetrahydro-benzo[4,5]imidazo[1,2-*c*]pyrimidin-1-ylsulfanyl)-acetic acid ethyl ester (**229a**)[63] and (3, 3,4a,7-tetramethyl-3,4,4a,5-tetrahydro-benzo[4,5]imidazo[1,2-*c*]pyrimidin-1-ylsulfanyl)-acetic acid ethyl ester (**229b**)[57] respectively. Acetylation of (**228a,c**) was carried out by refluxing with acetic anhydride/acetic acid to provide *N*-acetylated products 1-(3,3,4a-trimethyl-1-thioxo-2,3,4,4a-tetrahydro-1*H*-benzo[4,5]imidazo[1,2-*c*]pyrimidin-5-yl)-ethanone (**230a**) and 1-(7-methoxy-3,3,4a-trimethyl-1-thioxo-2,3,4,4a-tetrahydro-1*H*-benzo-[4,5]imidazo[1,2-*c*] pyrimidin-5-yl)-ethanone (**230c**) respectively.[57] When pyrimidobenzimidazole derivative (**228a**) was heated with 75% H_2SO_4, it was rearranged to *N*-(4,4,6-trimethyl-4*H*-[1,3]thiazin-2-yl)-benzene-1,2-diamine (**231**), as similar to the acid catalyzed rearrangement of pyrimidine thione to thiazine.[57] On heating with methanol containing sulfuric acid (pH = 1), compound (**228a**) gave the S-methylated derivative (i.e., 3,3,4a-trimethyl-1-methylsulfanyl-3,4,4a,5-tetrahydro-benzo[4,5]imidazo [1,2-*c*]pyrimidine) (**232**).[138] 4,5-Dimethyl-1,2-phenylenediamine (**233a**) on condensation with DMO-ITC (**1**) by refluxing in methanol at pH = 5, gave 3,3,4a,7,8-pentamethyl-3,4,4a,5-tetrahydro-2*H*-benzo[4,5]imidazo[1,2-*c*]pyrimidine-1-thione (**234a**). Similarly, 4-chloro-1,2-phenylenediamine (**233b**) reacted with DMO-ITC (**1**) at pH = 5 gave 7-chloro-3,3,4a-trimethyl-3,4,4a,5-tetrahydro-2*H*-benzo[4,5]imidazo[1,2-*c*]pyrimidine-1-thione (**234b**)[56] (Scheme 35).

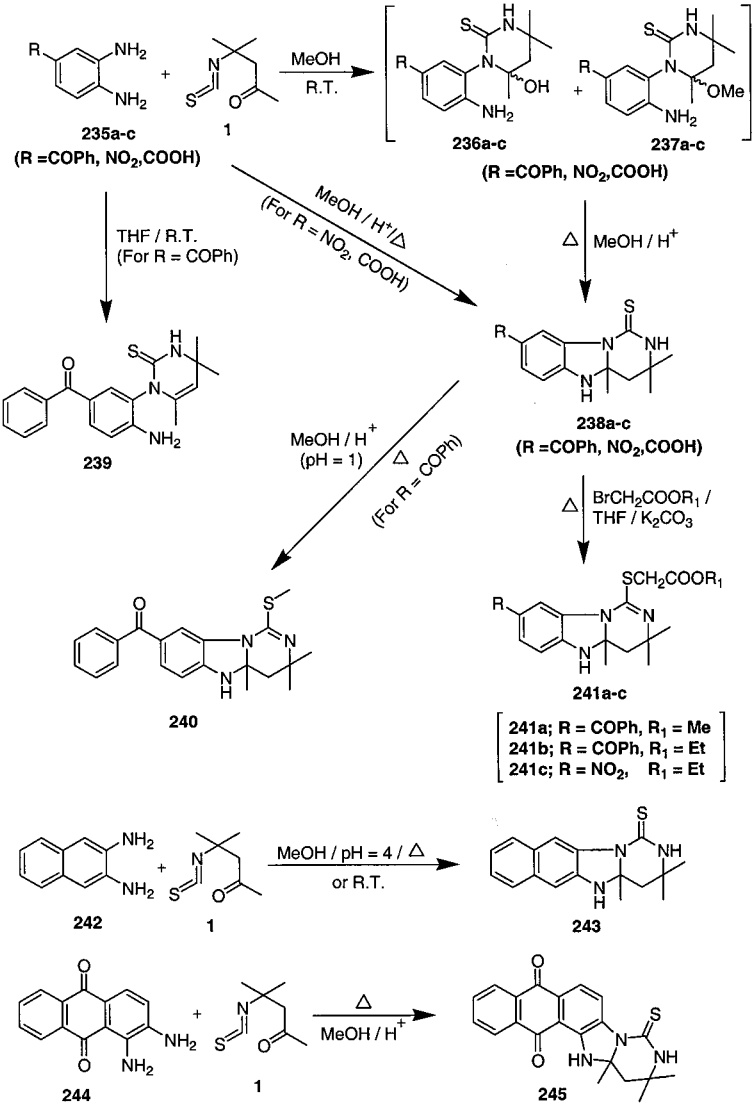
3,4-Diaminobenzophenone (**235a**) on condensation with DMO-ITC (**1**) in methanol at room temperature gave a mixture of hydroxy and methoxy derivatives, [4-amino-3-(6-hydroxy-4,4,6-trimethyl-2-thioxo-tetrahydro-pyrimidin-1-yl)-phenyl]-phenyl-methanone (**236a**),



SCHEME 35

and [4-amino-3-(6-methoxy-4,4,6-trimethyl-2-thioxo-tetrahydro-pyrimidin-1-yl)-phenyl]-phenyl-methanone (**237a**), respectively, which on heating with methanol under reflux at pH = 3 to 4 get cyclized and phenyl-(3,3,4a-trimethyl-1-thioxo-1,2,3,4,4a,5-hexahydro-benzo[4,5]imidazo[1,2-*c*]pyrimidin-8-yl)-methanone (**238a**) was obtained.[59,65] Similarly, 4-nitro-1,2-phenylenediamine (**235b**) reacted with DMO-ITC (**1**) in methanol at room temperature and gave

the mixture of 1-(2-amino-5-nitro-phenyl)-6-hydroxy-4,4,6-trimethyl-tetrahydro-pyrimidine-2-thione (**236b**) and 1-(2-amino-5-nitro-phenyl)-6-methoxy-4,4,6-trimethyl-tetrahydro-pyrimidine-2-thione (**237b**) which were cyclized to 3,3,4a-trimethyl-8-nitro-3,4,4a,5-tetrahydro-2*H*-benzo[4,5]imidazo[1,2-*c*]pyrimidine-1-thione (**238b**) when refluxed at pH = 3 to 4 in methanol.[61] 3,4-Diaminobenzoic acid (**235c**) also underwent a similar reaction with DMO-ITC (**1**) to produce the mixture of 4-amino-3-(6-hydroxy-4,4,6-trimethyl-2-thioxo-tetrahydro-pyrimidin-1-yl)-benzoic acid (**236c**) and 4-amino-3-(6-methoxy-4,4,6-trimethyl-2-thioxo-tetrahydro-pyrimidin-1-yl)-benzoic acid (**237c**) which were cyclized to 3,3,4a-trimethyl-1-thioxo-1,2,3,4,4a,5-hexahydro-benzo[4,5]imidazo[1,2-*c*]pyrimidine-8-carboxylic acid (**238c**) on refluxing at pH = 5 in methanol.[56] The same products (**238b**,**c**) also were obtained by direct condensation of 4-nitro-1,2-phenylenediamine (**235b**) and 3,4-diaminobenzoic acid (**235c**) with DMO-ITC (**1**), respectively,[62,56] by refluxing in methanol at pH = 4 to 5. On the other hand, the condensation of 3,4-diaminobenzophenone (**235a**) with DMO-ITC (**1**) in tetrahydrofuran (THF) as solvent gave [4-amino-3-(4,4,6-trimethyl-2-thioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-phenyl]-phenyl-methanone (**239**).[59] When compound (**238a**) was heated in methanol containing sulfuric acid (i.e., the pH of the reaction was 1), the S-methylated derivative phenyl-(3,3,4a-trimethyl-1-methylsulfanyl-3,4,4a,5-tetrahydro-benzo[4,5]imidazo[1,2-*c*]pyrimidin-8-yl)-methanone (**240**) was obtained.[59] Pyrimido benzimidazole derivative (**238a**) on refluxing with methylbromoacetate and ethylbromoacetate in the presence of potassium carbonate using tetrahydrofuran (THF) as solvent gave S-alkylated products; (8-benzoyl-3,3,4a-trimethyl-3,4,4a,5-tetrahydro-benzo[4,5]imidazo[1,2-*c*]pyrimidin-1-ylsulfanyl)-acetic acid methyl ester (**241a**) and (8-benzoyl-3,3,4a-trimethyl-3,4,4a,5-tetrahydro-benzo[4,5]imidazo[1,2-*c*]pyrimidin-1-ylsulfanyl)-acetic acid ethyl ester (**241b**) respectively.[59,65] Similarly, (**238b**) on refluxing with ethylbromoacetate in the presence of K_2CO_3 using tetrahydrofuran (THF) as solvent gave S-alkylated product (i.e., (3,3,4a-trimethyl-8-nitro-3,4,4a,5-tetrahydro-benzo[4,5]imidazo[1,2-*c*]pyrimidin-1-yl-sulfanyl)-acetic acid ethyl ester) (**241c**).[57] Condensation of 2,3-diaminonaphthalene (**242**) with DMO-ITC (**1**) either at reflux temperature of methanol containing an acid (pH = 4) or at room temperature gave 3,3,4a-trimethyl-3,4,4a,5-tetrahydro-2*H*-naphtho-[2′,3′:4,5]imidazo[1,2-*c*]pyrimidine-1-thione (**243**).[57] The reaction of DMO-ITC (**1**) with 1,2-diaminoanthraquinone (**244**) at reflux temperature in methanol using catalytic amount of sulfuric acid (pH = 1) gave 2,2,13a-trimethyl-4-thioxo-1,2,3,4,13,13a-hexahydro-3,4a,13-triaza-indeno[2,1-*a*]anthracene-7,12-dione (**245**).[61,65] (Scheme 36).

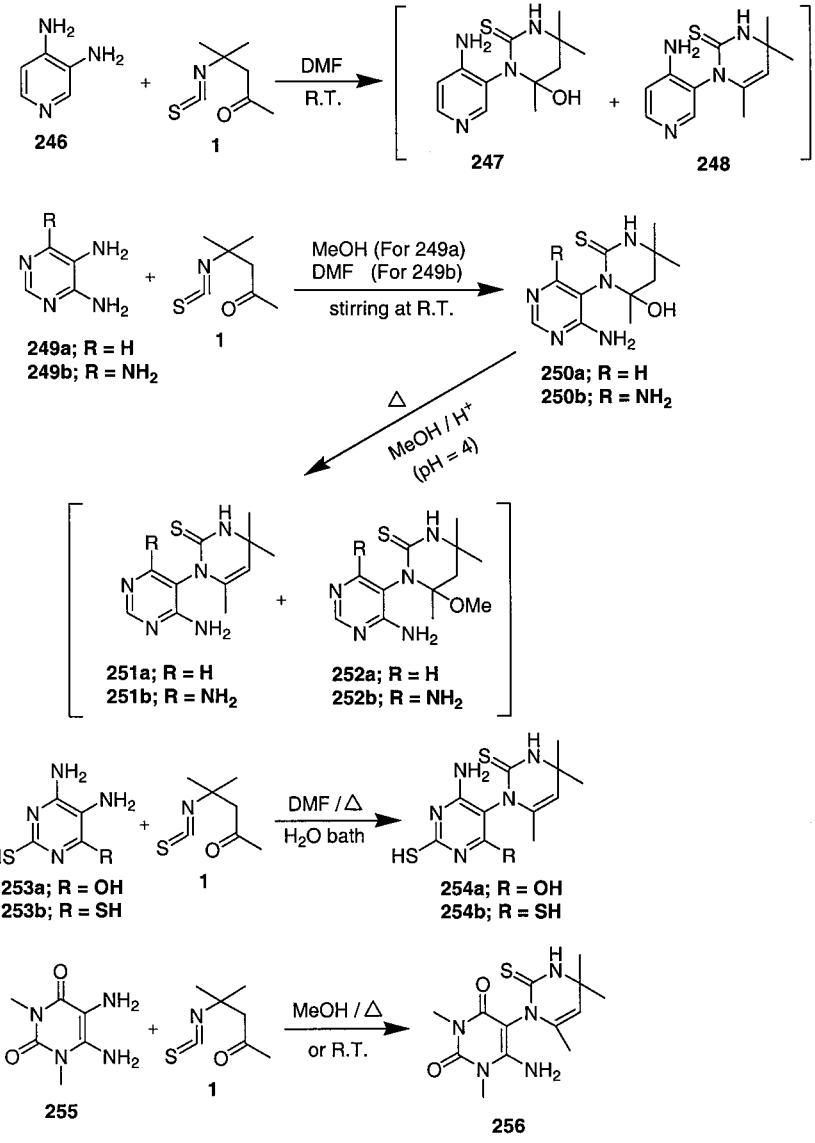


SCHEME 36

Heterocyclic Diamines

The condensation reaction of 3,4-diaminopyridine (**246**) with DMO-ITC (**1**) in dimethylformamide (DMF) at room temperature gave two condensed products 1-(4-amino-pyridin-3-yl)-6-hydroxy-4,4,

6-trimethyl-tetrahydro-pyrimidine-2-thione (**247**) and 1-(4-amino-pyridin-3-yl)-4,4,6-trimethyl-3,4-dihydro-1*H*-pyrimidine-2-thione (**248**), respectively, in which (**247**) was found to be the major product. Reaction of 5,6-diaminopyrimidine (**249a**) with DMO-ITC (**1**) at room



SCHEME 37

temperature in methanol gave 4′-amino-6-hydroxy-4,4,6-trimethyl-3,4,5,6-tetrahydro-[1,5′]bipyrimidinyl-2-thione (**250a**). Condensation of 4,5,6-triaminopyrimidine sulfate (**249b**) with DMO-ITC (**1**) in dimethylformamide (DMF) at 100°C gave 4′,6′-diamino-6-hydroxy-4,4,6-trimethyl-3,4,5,6-tetrahydro-[1,5′]bipyrimidinyl-2-thione (**250b**). When compounds (**250a**) and (**250b**) were heated under reflux in methanol at pH = 4, cyclization was not done and only the mixture of 4′-amino-4,4,6-trimethyl-3,4-dihydro-[1,5′]bipyrimidinyl-2-thione (**251a**), and 4′-amino-6-methoxy-4,4,6-trimethyl-3,4,5,6-tetrahydro-[1,5′] bipyrim-idinyl-2-thione (**252a**), as well as 4′,6′-diamino-4,4,6-trimethyl-3,4-dihydro-[1,5′]bipyrimidinyl-2-thione (**251b**), and, 4′,6′-diamino-6-methoxy-4,4,6-trimethyl-3,4,5,6-tetrahydro-[1,5′]bipyrimidinyl-2-thione (**252b**) were obtained respectively. Condensation of 4,5-diamino-6-hydroxy-2-mercapto pyrimidine (**253a**) with DMO-ITC (**1**) in dimethylformamide (DMF) at 100°C gave 6′-amino-4′-hydroxy-2′-mercapto-4,4,6-trimethyl-3,4-dihydro-[1,5′]bipyrimidinyl-2-thione (**254a**). Similarly, the condensation of 4,5-diamino-2,6-dimercapto pyrimidine (**253b**) with DMO-ITC (**1**) gave 6′-amino-2′,4′-dimercapto-4,4,6-trimethyl-3,4-dihydro-[1,5′]bipyrimidinyl-2-thione (**254b**). Condensation of 5,6-diamino-1,3-dimethyl uracil hydrate (**255**) with DMO-ITC (**1**) in methanol at 65°C or 25°C gave compound 6′-amino-4,4,6,1′,3′-pentamethyl-2-thioxo-3,4-dihydro-2H,1′*H*-[1,5′]bipyrimidinyl-2′,4′-di-one (**256**)[56] (Scheme 37).

CONCLUSION

1,1-Dimethyl-3-oxobutyl-isothiocyanate (DMO-ITC) has been proved to be an important starting material for the construction of heterocycles with promising potentials in medicinal chemistry. Therefore, more study is required for the reactions of DMO-ITC (**1**) with new substrates. On the other hand, the desulfurization reaction of DMO-ITC (**1**) derived heterocycles could be profitably exploited in the preparation of those compounds having carbonyl in the place of thiocarbonyl group, which would eliminate the use of particularly harmful isocyanate. In short, it may be concluded that the knowledge gained about the reactions of DMO-ITC (**1**) over the last 55 years has provided some dividends in the area of medicinal chemistry.

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