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Review Article

SYNTHESIS AND BIOLOGICAL EVALUATION OF 1,3-THIAZINES- A REVIEW

Simerpreet and **Cannoo Singh Damanjit***

Department of Chemistry

Sant Longowal Institute of Engineering and Technology, Longowal, Sangrur-148106, Punjab, India

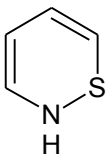
ABSTRACT

The multifaceted chemical potential of 1, 3-thiazine- a six membered motif/species containing nitrogen and sulphur in the ring has led to unabated research in their synthetic methodologies. This paper summarizes various methods viz. condensation, cyclo-addition, ring transformations etc. to procure 1,3-thiazines and their derivatives along with biological activities viz. pharmacological and agrochemical etc.

Keywords: 1, 3-Thiazine, Condensation, Ring transformation, Antimicrobial, Insecticidal activity.

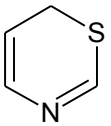
INTRODUCTION

Organic compounds play a vital role in modern society and posses varied applications in different fields due to which unabated research has been going on to synthesize new organic compounds including derivatization of naturally occurring ones- nucleic acids, plant alkaloids, some vitamins, proteins, hormones etc. Synthetic heterocyclic compounds especially containing heteroatom N, S, O have enormous potential primarily as agrochemicals, drugs etc.. Thiazine- a heterocyclic compound having four carbon atoms and one nitrogen and sulphur atom at varied positions in the six membered ring exist as 1,2; 1,3; 1,4-thiazines (1-3) and subsequently their derivatives having N-C-S linkage have been used as antitubercular, antibacterial, antimicrobial, antitumor, insecticidal, fungicidal, herbicidal agents, tranquilizers and various dyes etc.[2, 4, 6, 12, 13, 15-19] Further, 1,3-thiazine core moieties have remarkable potential of anti radiation agents.[2] 1,3-Thiazines are used in various organic synthesis and transformations as reaction intermediates.[2, 15] This paper mainly focuses on different synthetic procedures along with biological activities of 1,3-thiazines and their derivatives.



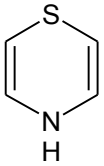
1,2-Thiazine

(1)



1,3-Thiazine

(2)

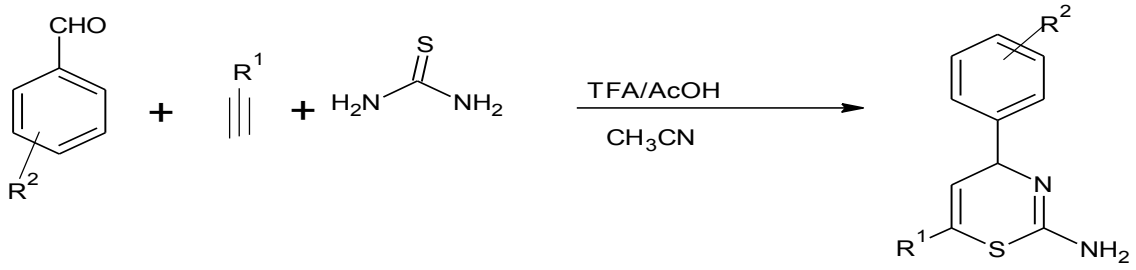


1, 4-Thiazine

(3)

1 For the synthesis of 1,3-thiazines, thiourea has been the major reactant in most of the synthetic procedures. Sulphur and nitrogen of thiourea have been placed in 1,3-thiazine ring by various cyclo-condensation, ring transformation, addition reactions etc. with different reactants to produce variety of 1,3-thiazines.

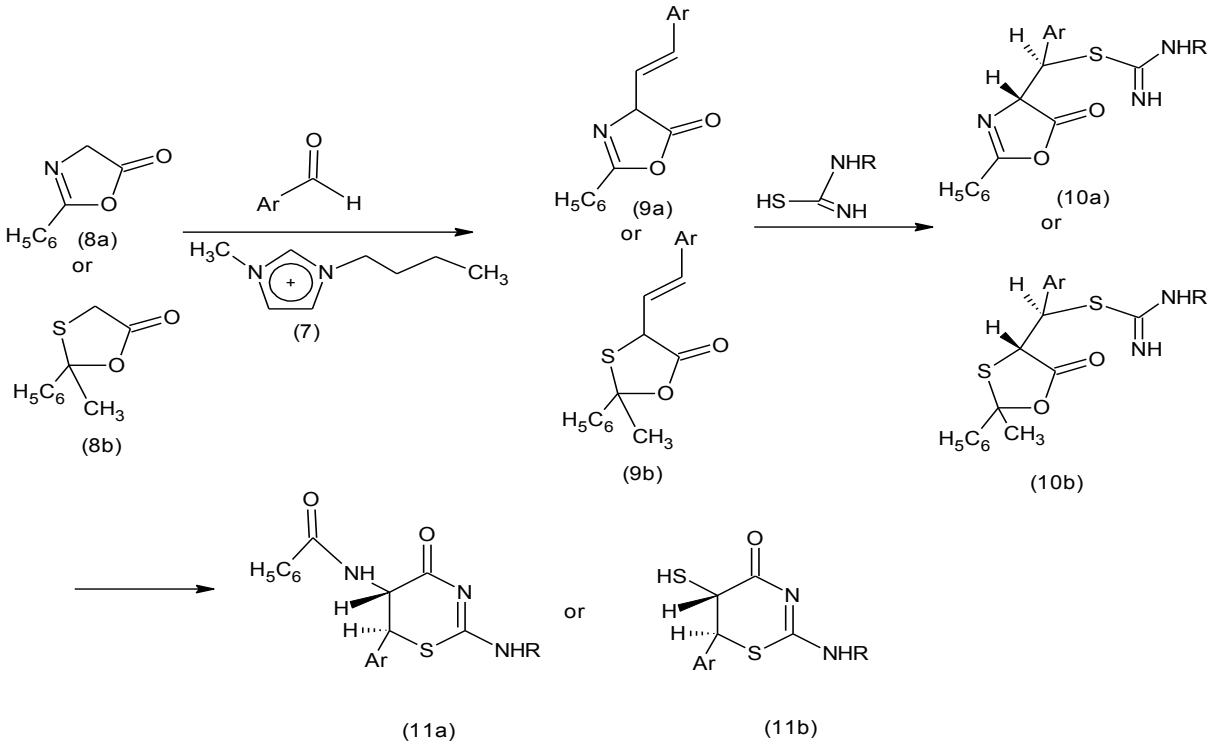
One pot reaction of aryl aldehydes (4) with thiourea (5) give 4H-1,3-thiazine derivative (6) in excellent yield.[1]



(4) (5) (6)

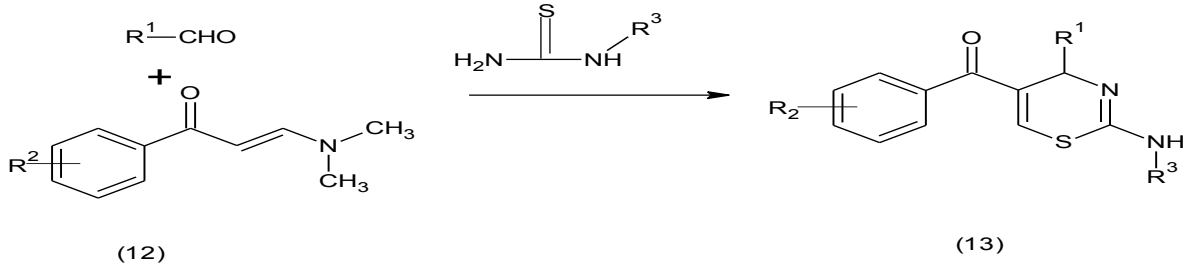
R^1= -C_6H_5, p-F-C_6H_5; R^2= -H, p-CH_3, p-F, p-CH_3O, p-Cl, p-NO_2, m-NO_2

1-Butyl-3-methyl-1H-imidazol-3-ium bromide ([Bmim]Br) (7) promoted Knoevenagel condensation of aromatic aldehyde with masked amino acid, 2-phenyl-1,3-oxazol-5-one (8a) and mercapto acid, 2-methyl-2-phenyl-1,3-oxathiolan-5-one (8b) to yield 4-benzylidene-2-phenyloxazol-5-one (9a) and 4-benzylidene-2-methyl-2-phenyl-1,3-oxathiolan-5-one (9b) respectively. These (9a, 9b) on treatment with thiourea gives Michael adduct (10a, 10b) which undergo ring transformation to produce diasteromer of 2,5-diamino-1,3-thiazine-4-ones (11a) or 2-amino-5-mercapto-1,3-thiazine-4-ones (11b).[2]



Ar= -C_6H_5, p-Cl-C_6H_4, p-CH_3O-C_6H_4, p-$(CH_3)_2N$-C_6H_4; R= -H, -C_6H_5

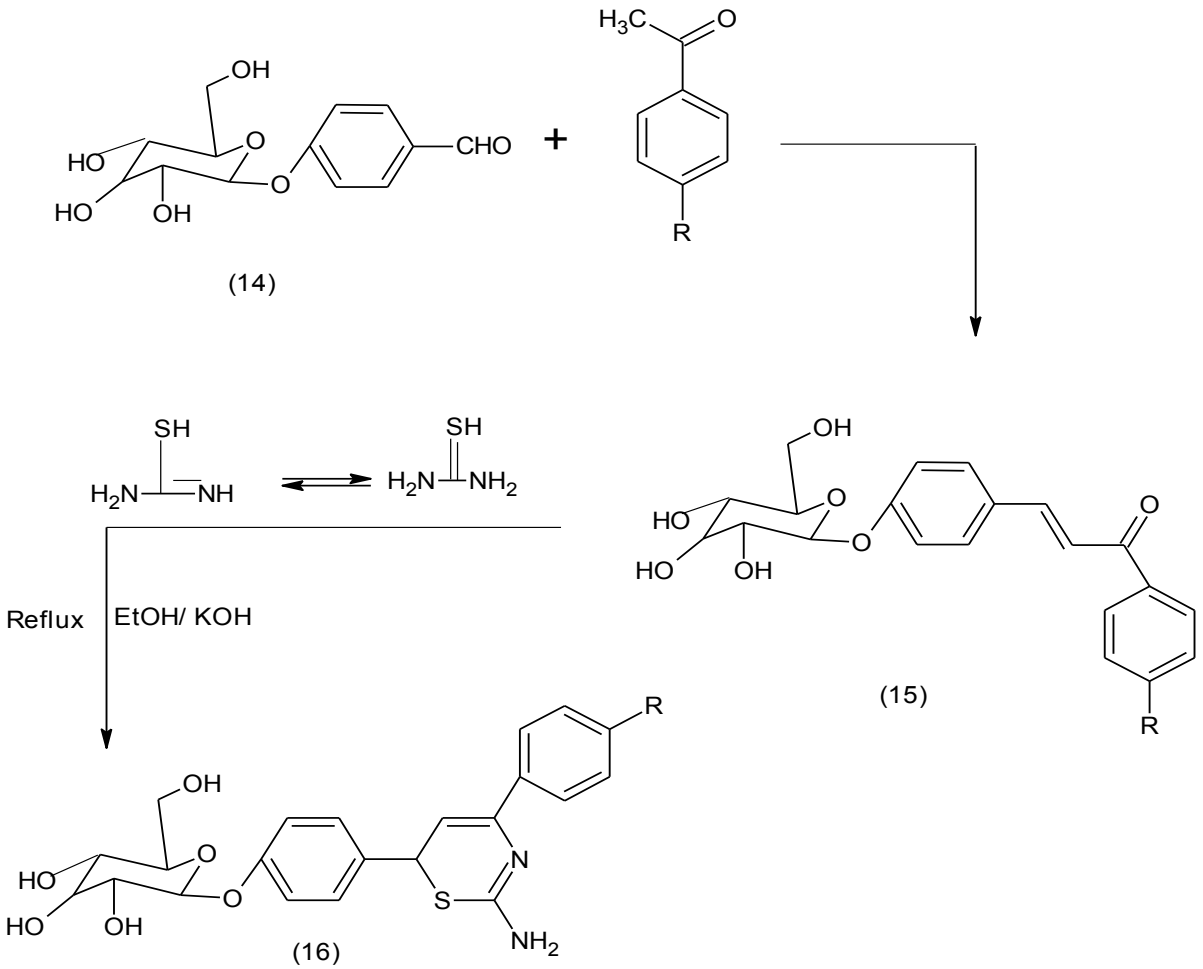
Multicomponent reaction of aldehydes, enaminone (12) and thiourea in the presence of trimethyl silyl chloride (TMSCl) yield substituted 1,3- thiazine derivatives (13).[3]



(12) (13)

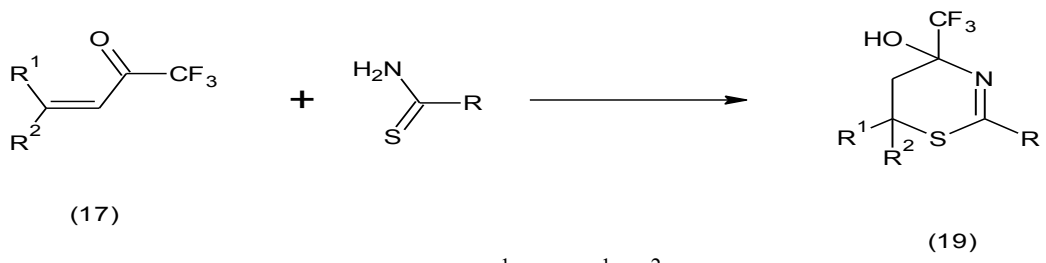
R^1= alkyl, aryl; R^2=R^3= -H, alkyl, aryl.

Helicid [4-formylphenyl-β-D-allopyranoside] (14) condensed with 4-substituted acetopheno-ne to give E-(4-β-D-allopyranosyloxyphenyl)-1-(4-substituted phenyl) propenone derivatives (15). the latter undergo 1,4-Michael addition with thiourea in basic medium to yield 6H-2-amino-4-aryl-6-(4-β-D-allopyranosyloxyphenyl)-1,3-thiazine derivatives (16).[4]

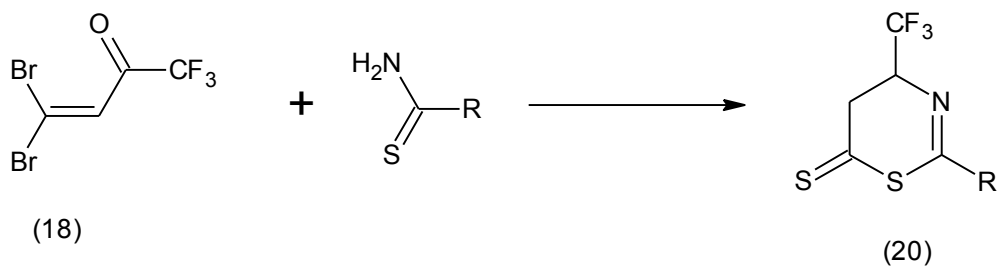


R=-H, -CH_3, -OCH_3, -Cl, -Br, -F, -C_2H_5

On refluxing trifluoromethyl enones (17)/ β,β- dibromo-CF_3-ketones (18) with thiourea or thioacetamide in acidic medium give dihydrothiazines (19) or 1,3-thiazine derivatives (20).[5]

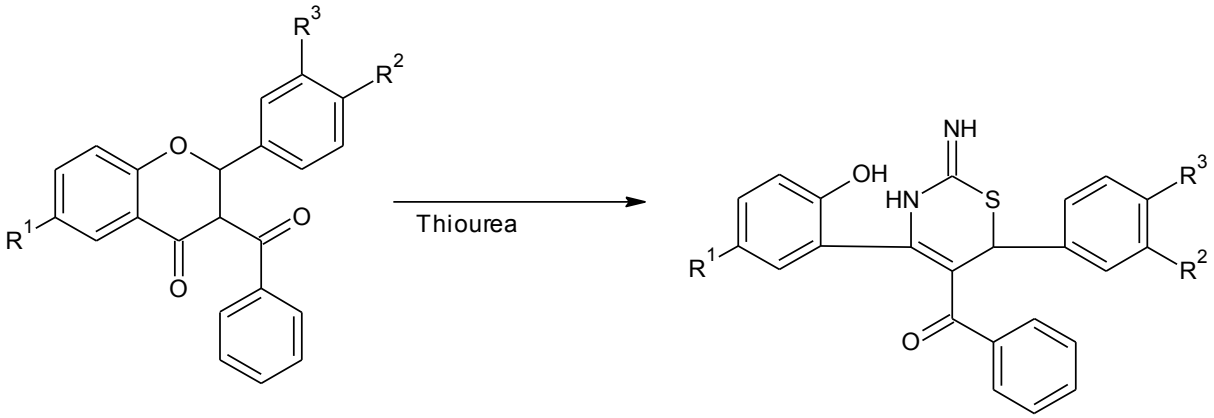


R=-NH_2, -CH_3; R^1=-H; R^1=R^2=-$(CH_3)_2$



R= -NH_2, -CH_3

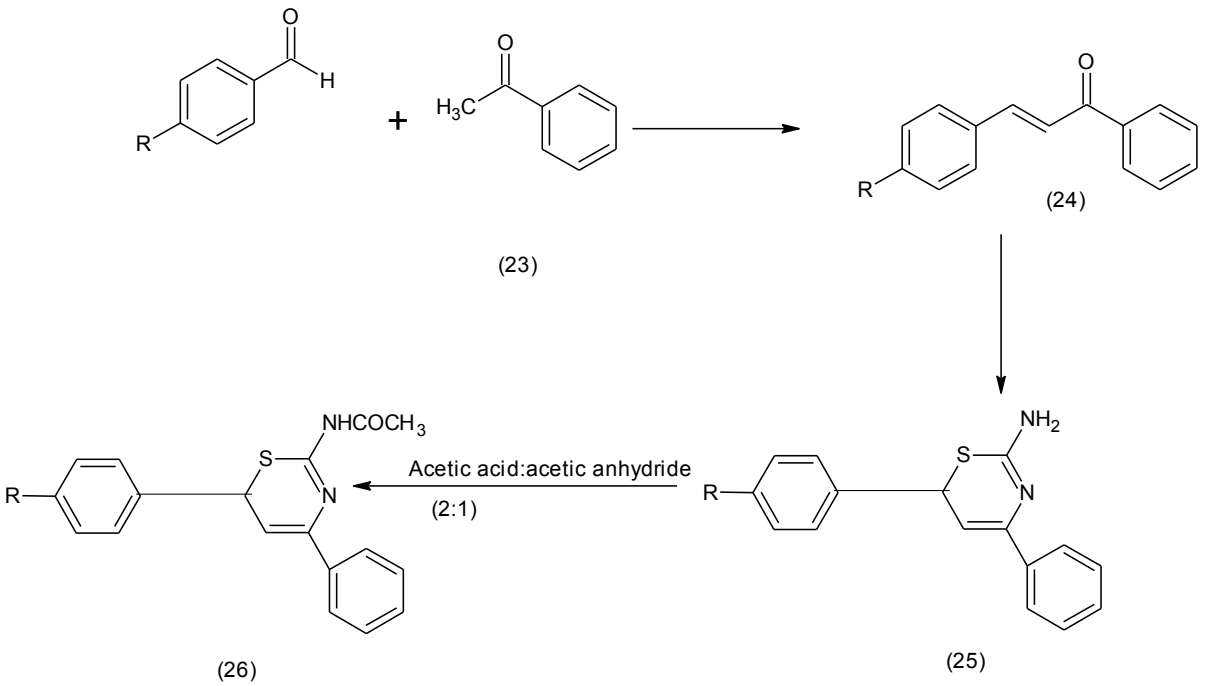
3-Benzoyl-3,4,6-trisubstituted flavanones (21) procured from 1-(2-hydroxyphenyl)-3,5-disubstituted-1,3-propandione and benzaldehyde when refluxed with thiourea in dry pyridine affords 4-(2-hydroxy-5-substitutedphenyl)-5-benzoyl-6-substitutedphenyl-2-imino-6H-2,3-dihydro-1,3-thiazine derivatives (22).[6]



(21) (22)

R^1=R^2=R^3=-H; R^1=R^3=-H, R^2=-OCH_3; R^2=R^3=-OCH_3; R^1=R^3=H, R^2=-$N(CH_3)_2$; R^1=-CH_3, R^2=R^3=-H; R^1=-CH_3, R^2=-OCH_3, R^3=-H; R^2=R^3=-OCH_3, R^1=-CH_3; R^1=-CH_3, R^2=-$N(CH_3)_2$, R^3=-H.

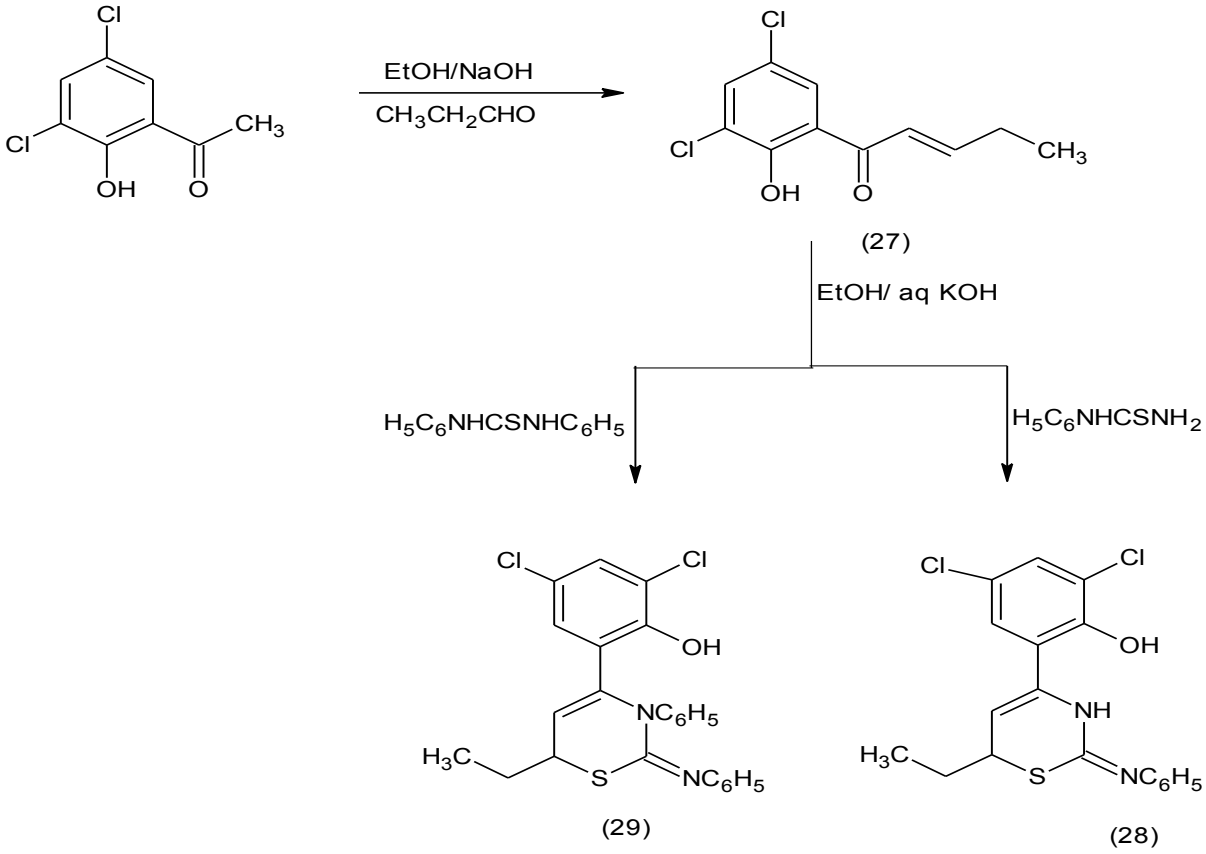
Claisen- Schmidt condensation of acetophenone (23) and aryl aldehydes yields chalcone derivatives (24) which on treatment with thiourea undergo cyclization in basic medium to yield 6-[4-substituted phenyl]-4-phenyl-6H-1,3-thiazine-2-amine derivatives (25). The latter can be acylated to give N-[6-(4-substituted phenyl)-4-phenyl-6H-1,3-thiazine-yl] acetamide derivatives (26).[7]

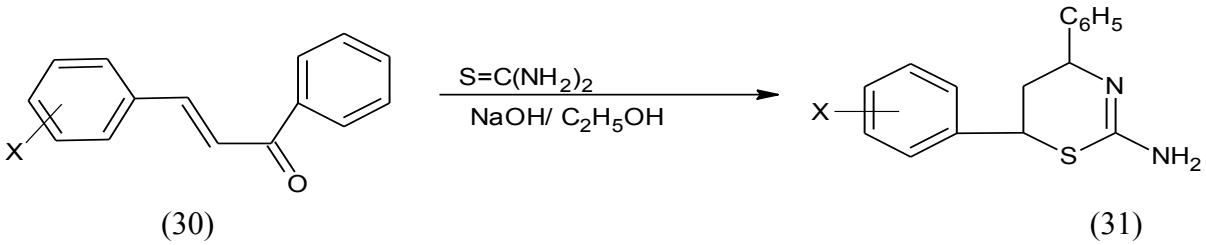


(23) (24) (26) (25)

R= -CH_3, -N (CH_3)$_2$, -Cl, -NO_2, -OCH_3, -OH

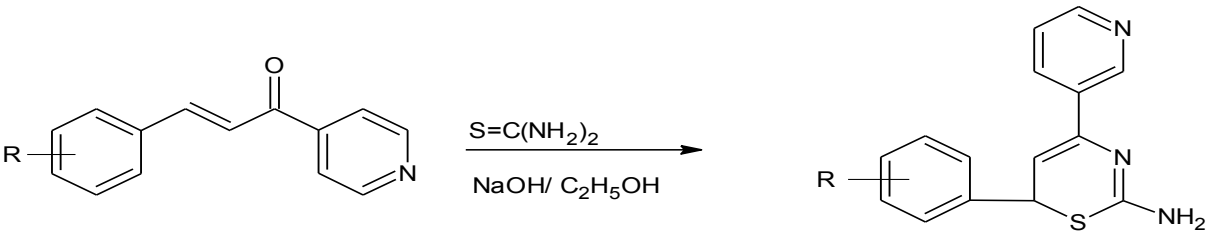
Similarly, 2-hydroxy-3,5-dichloro-4-ethyl chalcone (27) when treated with phenylthiourea and diphenyl thiourea gives 4-(2'-hydroxy-3',5'-dichlorophenyl)-6-(ethyl)-2-iminophenyl-1,3-thiazine (28) and 4-(2'-hydroxy-3',5'-dichlorophenyl)-6-(ethyl)-2-iminophenyl-3-phenyl-1,3-thiazine (29) respectively.[8] Further, mono and di-substituted chalcone derivatives (30, 32, 34) when stirred with thiourea under similar conditions yield the corresponding 1,3-thiazine derivatives (31, 33, 35).[9, 10, 11]





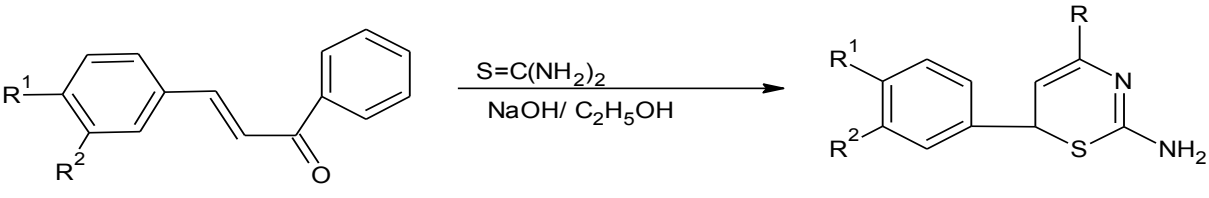
(30) (31)

X= o-OH; p-$N(CH_3)_2$; m-OCH_3



(32) (33)

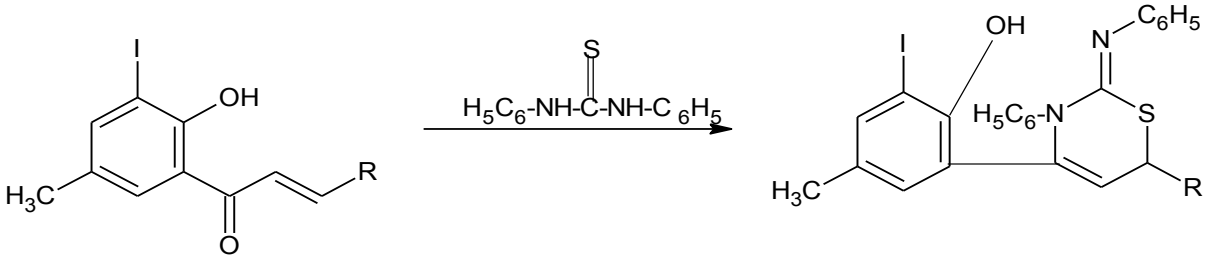
R= m-NO_2, p-OH, m-Br, m-OCH_3, p-N $(CH_3)_2$



(34) (35)

R= -C_6H_5; R^1=-OCH_3, -H; R^2= -H, -Cl, -NO_2

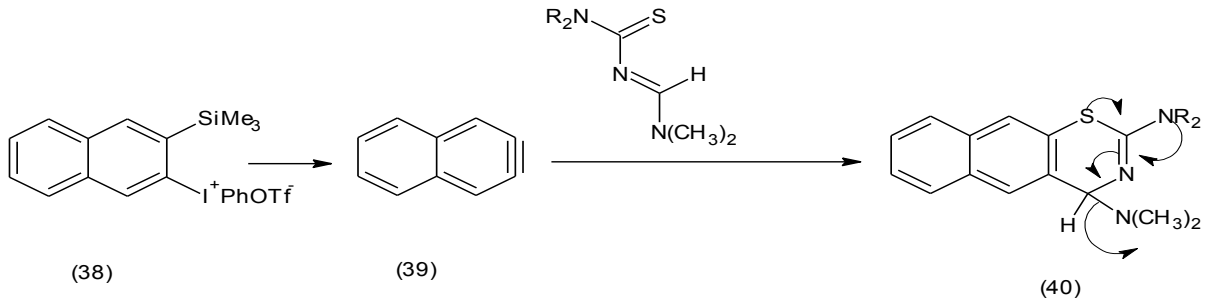
Furthermore, chalcone derivatives (36) on refluxing with diphenyl thiourea in basic medium with few drops of piperidine give 1,3-thiazine derivatives (37) in better yields.[12]



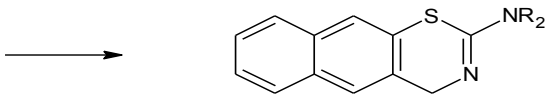
(36) (37)

R= -C_6H_5, -C_6H_5-OCH_3, -C_6H_5-Cl, -C_6H_5-OH, -HC=HC-C_6H_5, -C_4H_3O

(Phenyl)[3-trimethylsilyl)-2-naphthyl]iodonium triflate (38) on stirring with tetrahydrofuran solution of Bu_4NF at 0°C gives Diels Alder adduct-benzyne intermediate (39) which aromatized with N^1, N^1-disubstituted-N^2-(dimethylaminomethylidene) thiourea by electron release from S and NR_2 to give (40). The latter undergoes NMe_2 anion displacement and subsequent 1,3-hydride shift to provide disubstituted-amino-4H-naptho[2,3-e]-1,3-thiazine derivatives (41).[13]



(38) (39) (40)



(41)

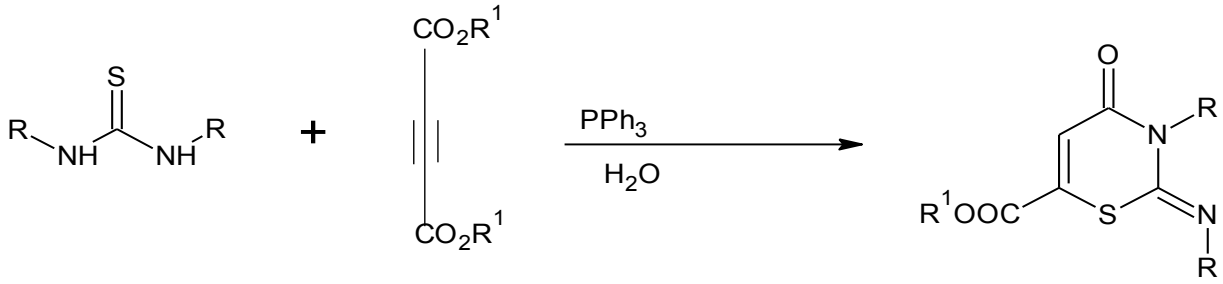
R=-C_2H_5, -$(CH_2)_4$, -$(CH_2)_5$, -CH-$(CH_2)_2O(CH_2)_2$

Allylic bromide (42) undergoes nucleophilic reaction and cyclization with thiourea in basic medium to yield 2-amino-1,3-thiazine-4-ones (43) through the intermediacy of isothiuronium salt.[14]

(42) (43)

R= -C_6H_5, p-CH_3O-C_6H_4, p-NO_2-C_6H_4, o-Cl-C_6H_4, o-$C_{10}H_7$, -CH_3, -CH_3CH_2.

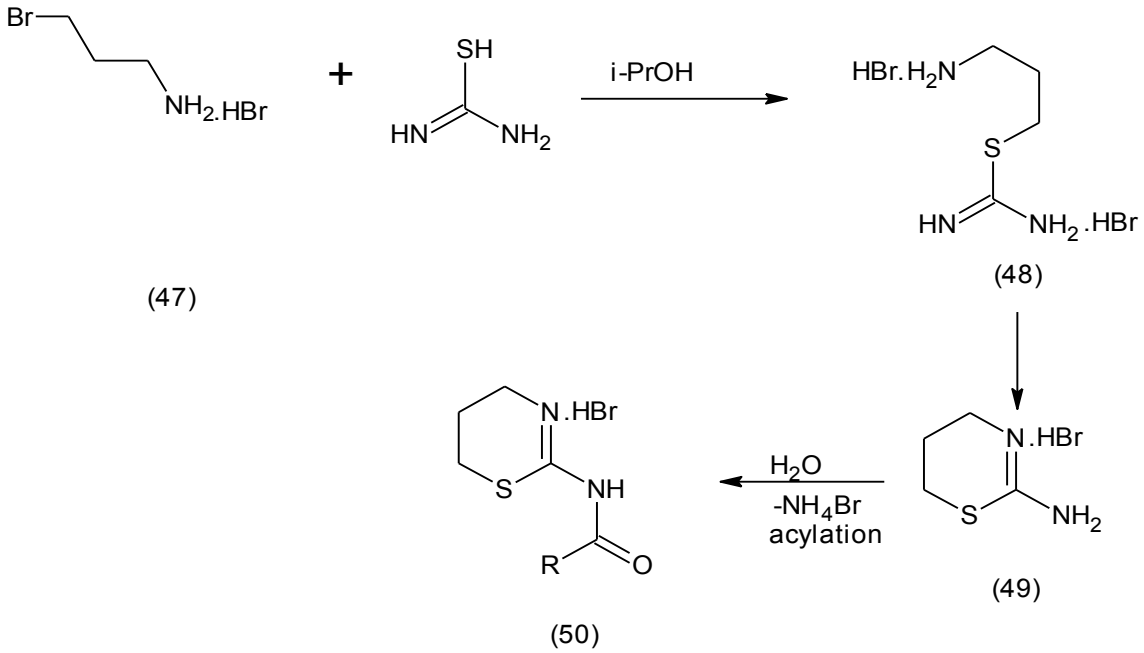
Dialkylthioureas (44) on treatment with electron deficient acetylenic esters (45) and triphenylphosphine as catalyst yield 2H-1,3-thiazine derivative (46).[15]



(44) (45) (46)

R=R[1]-C_6H_5, -C_2H_5

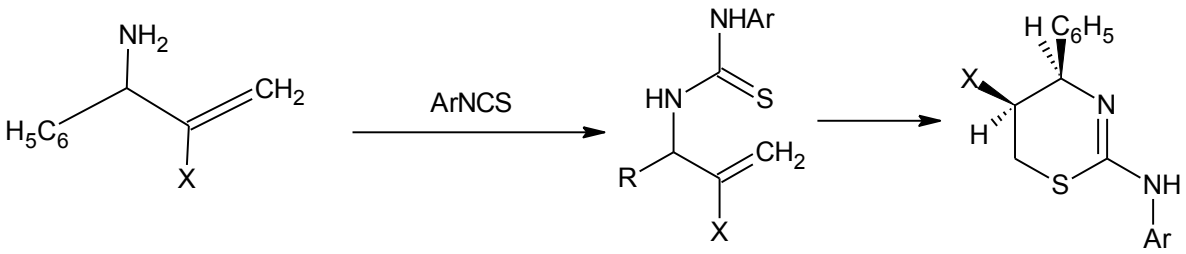
Cycloaddition of propylamine hydrobromide (47) with thiourea produces S-(aminopropyl) isothiourea dihydrobromide (48) which on heating cyclizes to 2-amino-5,6-dihydro-4H-1,3-thiazine (49). On acylation of the latter, 2-N-acylamino-5,6-dihydro-4H-1,3-thiazine hydrobromide (50) was obtained.[16]



(47) (48) (49) (50)

R=-CH_3, -C_6H_5, -Cyclohexyl, -adamantyl

Stereoselective synthesis of 2-susbstituted amino-5,6-dihydro-4H-1,3-thiazines (52) involves intramolecular cyclization by sulpha -Michael reaction of allyl thiourea (51) which in turn has been prepared from allylamine and arylisothiocyanate.[1]

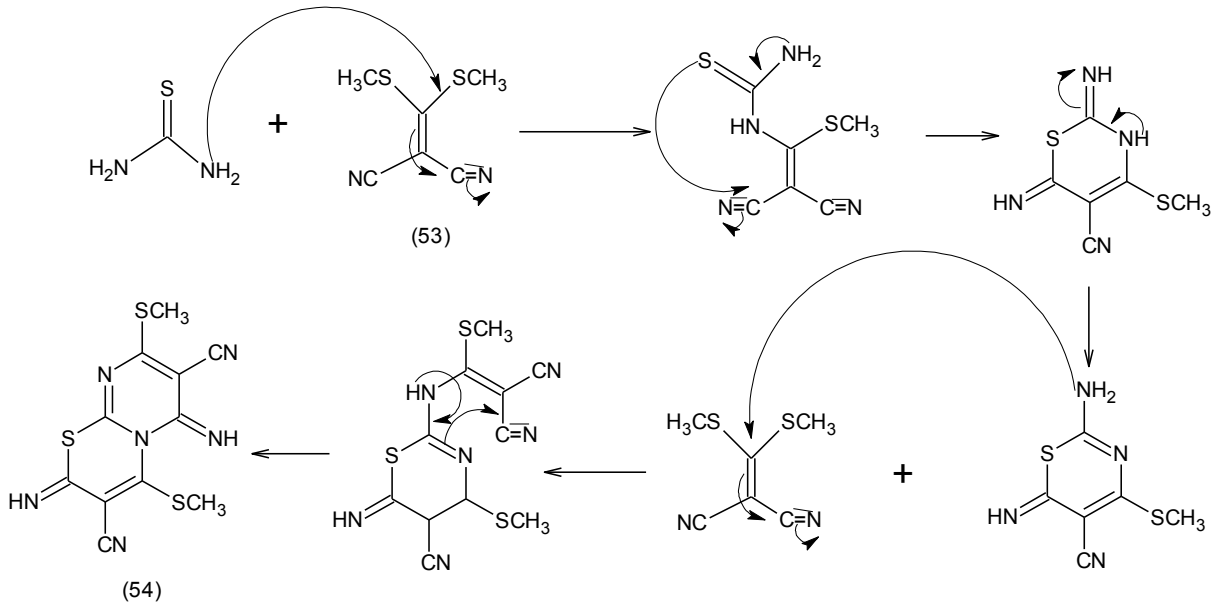


(51) (52)

X= -CO_2Me, -CN; Ar= -C_6H_5, p-ClC_6H_4, O-BrC_6H_4

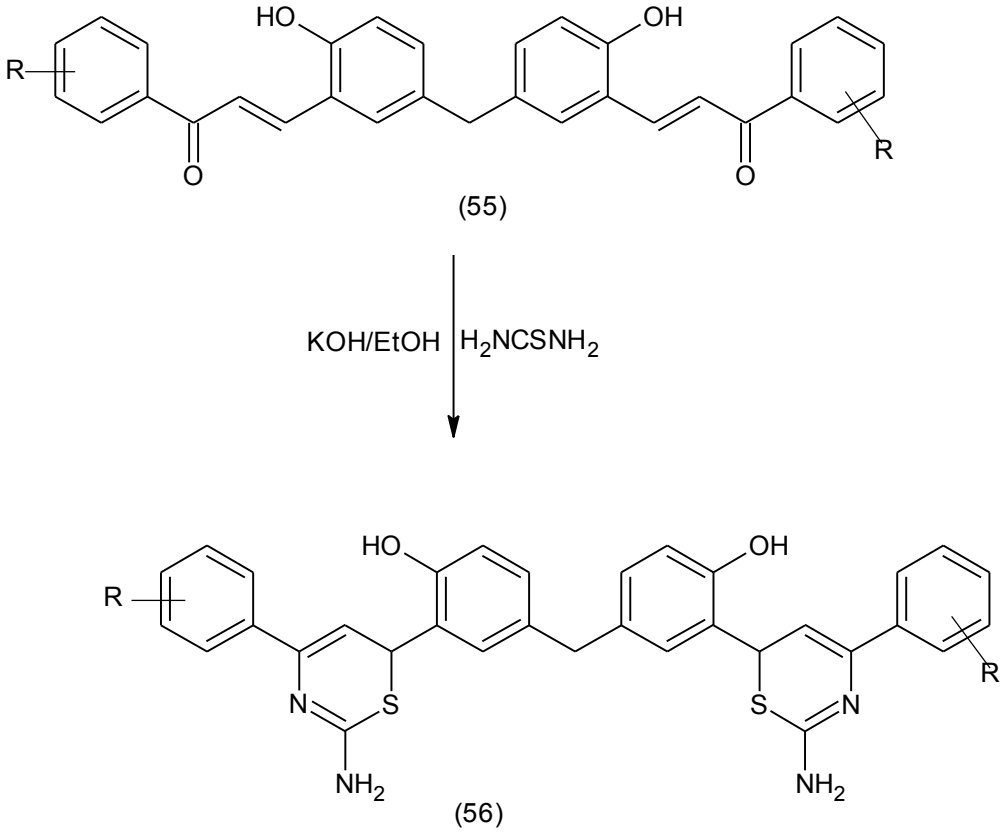
On refluxing (methylthio) methylene malanonitrile (53) with thiourea in the presence of anhydrous potassium carbonate for 12 hours produces 2,6-dihydro-2,6-diimino-4,8-bis(methylthio) pyrimido [2,1-

b][1,3] thiazine-3,7-dicarbonitrile (54). The proposed mechanism revealed that the latter having 2-methylthio group, an activated nitrogen and an electron withdrawing cyano group enhances the reactivity towards nucleophile to give substituted 1,3-thiazines (scheme-1).[18]



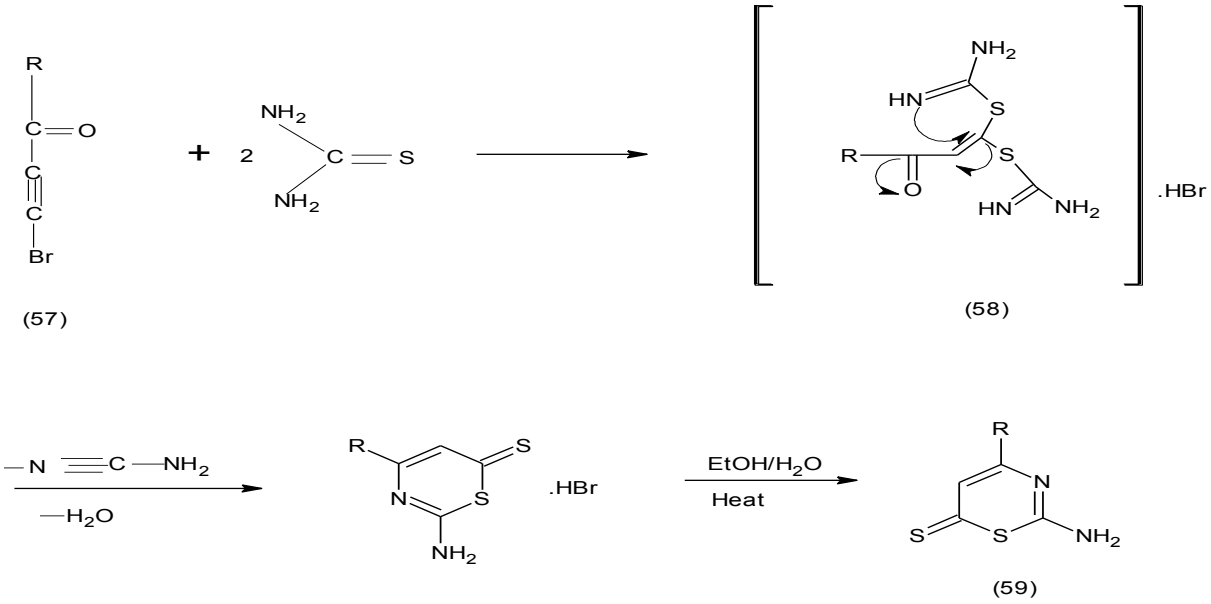
Scheme-1

Bis[3-[(E)-3(4-substitutedphenyl)-3-oxo-1-propenyl]-4-hydroxyphenyl] methane (55) on treating with thiourea followed by cyclization in ethanolic KOH produces bis- thiazine derivatives (56).[19]



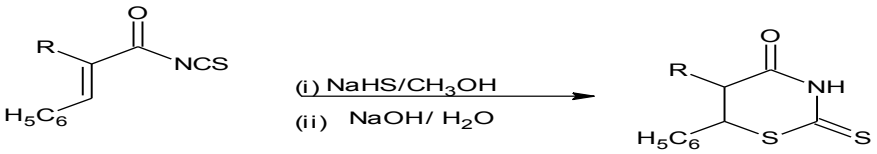
R= -H, p-OCH_3, p-Cl, p-NO_2, p-Br, o-Cl

1-Acyl-2-bromoacetylene derivatives (57) when treated with thiourea in the presence of glacial acetic acid produce α-oxoketene mercaptals (58). The latter in $BF_3.Et_2O$, with the removal of cyanamide and water undergoes intramolecular cyclization to give 1,3-thiazine-6-thione hydrobromide which on recrystallization with water-alcohol yields pure substituted 2-amino-1,3-thiazine-6-thiones (59).[20]



R= -C_6H_5, o-thienyl

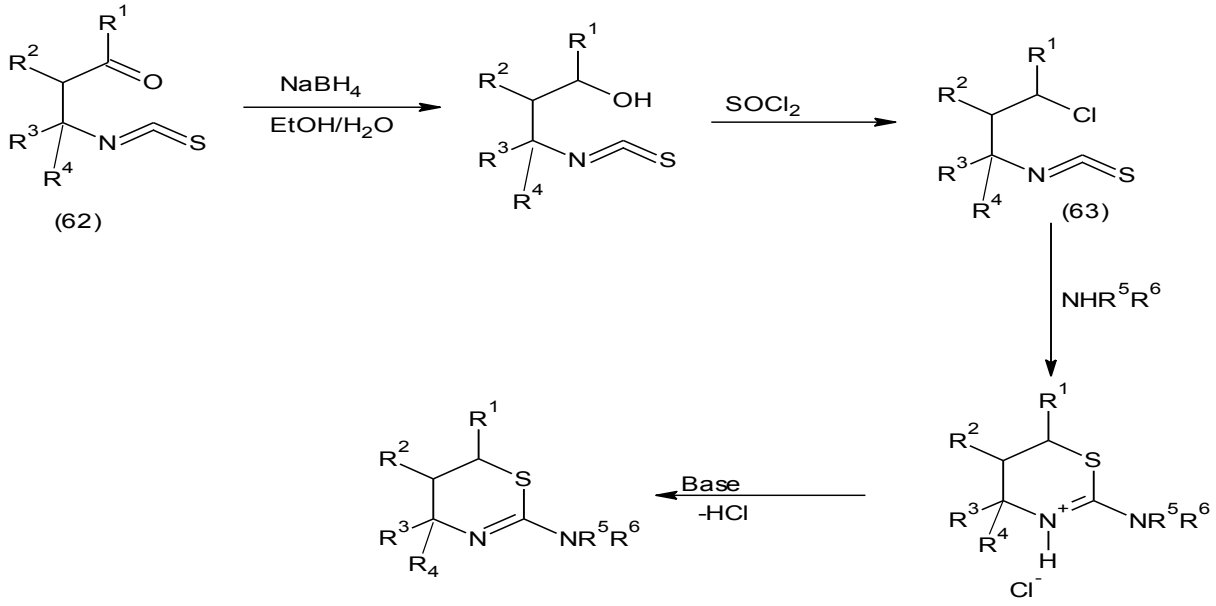
2. On stirring isothiocyanate (60) in methanol with solution of sodium hydrogen sulfide gives 2-substituted 3-phenyl-3-(thiocarbamoylthio)propanoate which by alternate cyclization in basic medium yields 5-substituted 6-phenyl-2-thioxo-tetrahydro-4H-1,3-thiazine-4-ones (61).[21]



(60) (61)

R= -H, -CH_3, -C_6H_5

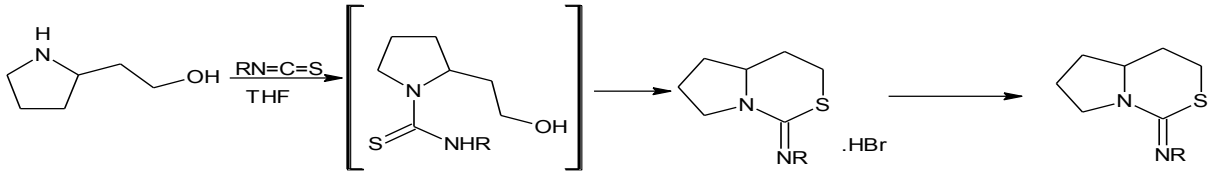
1,3-Isothiocyanato ketones (62) get reduced with $NaBH_4$ to give 1,3-isothiocyanato alcohols which subsequently react with thionyl chloride to produce 3-chloro-1-isothiocyanatoalkane derivatives (63). The latter in methanol and ammonia treated with NaOH yield 2-amino-4,4,6-trisubstituted-5,6-dihydro-4H-1,3-thiazine (64)(scheme-2).[22]



R^1=R^2=R^4=-H, R^3=-Me; R^1=R^2=-Me, R^3, R^4=-H; R^1=R^3=R^4=-Me, R^2=-H; R^1=R^2=R^3=R^4=-CH_3; R^5=R^6=H; R^5=-Bn, R^6=-H; R^1= -C_6H_5, t-Bu; R^2= -OCH_3, -H; R^3= -H, -OCH_3, -CH_3

Scheme-2

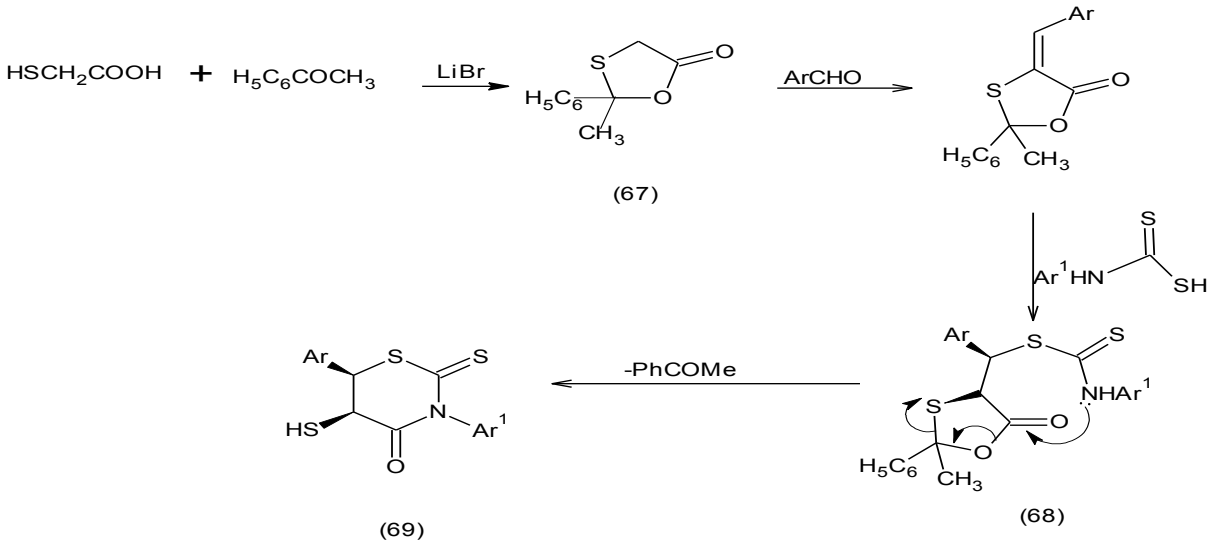
2-(β-Hydroxyethyl)-pyrrolidine (65) on refluxing with isothiocyanate derivative in THF gives an intermediate thiourea derivative which by intramolecular cyclization produces N-(3,4,4a,5,6,7-hexahydro-1H-pyrrolo[1,2-c][1,3]thiazin-1-ylidene (66).[23]



(65) (66)

R= -CH_3, -C_2H_5, cyclo-C_6H_{11}, -$CH_2C_6H_5$, -C_6H_4, p-CH_3-C_6H_4, p-CH_3O-C_6H_4, p-Br-C_6H_4, p-Cl-C_6H_4

One pot diasteroselective reaction of 2-methyl-2-phenyl-1,3-oxathiolan-5-one (67), aromatic aldehyde and N-aryldithiocarbamic acid in microwave yields Michael adduct (68). The latter undergo ring transformation to produce polyfunctionalised 3,6-diaryl-5-mercaptoperhydro-2-thioxo-1,3-thiazine-4-ones (69) (scheme-3).[24]

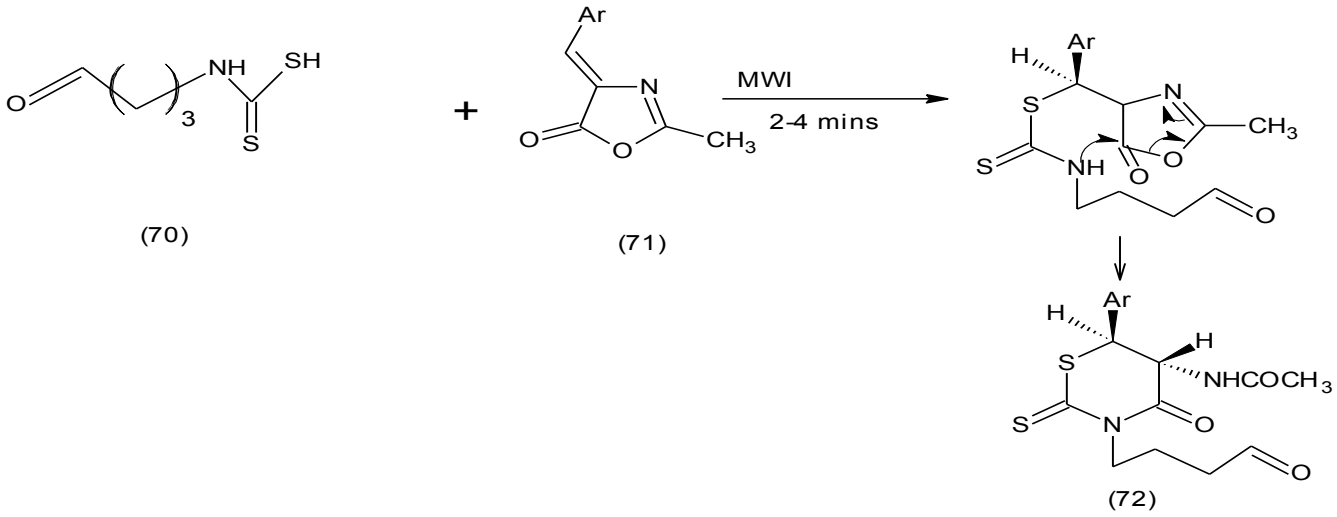


(67) (68) (69)

Ar= -Ph, p-Cl-C_6H_4, p-MeO-C_6H_4; Ar^1= -Ph, o-Me-C_6H_4, p-MeO-C_6H_4

Scheme-3

(4-Oxo-butyl)-dithiocarbamic acid (70) and 4-arylidene-5(4H)-oxozolones (71) in microwave with montmorillonite K-10 clay yield N-[3-(3-hydroxymethyl-4-oxo-butyl)-4-oxo-6-aryl-2-thioxo-[1,3]thiazinan-5-yl]-acetamide derivatives (72) (scheme-4).[25]

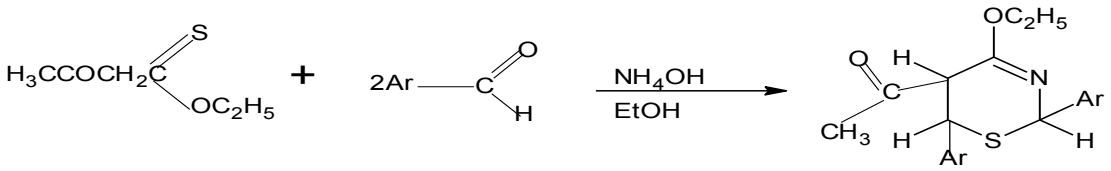


(70) (71) (72)

Ar= -C_6H_5, p-CH_3O-C_6H_4, p-HO-C_6H_4, p-Cl-C_6H_4, p-NO_2-C_6H_4

Scheme-4

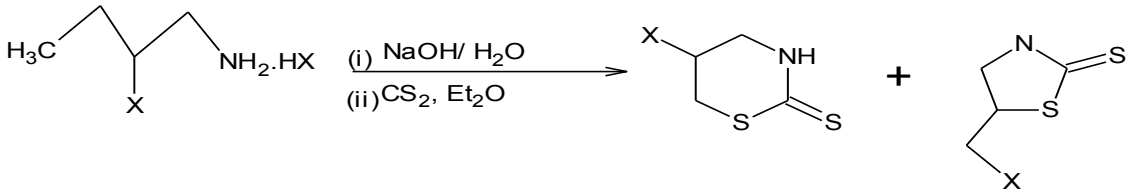
4. Cyclocondensation of acetothioacetic acid-O-ethyl ester (73) with aromatic aldehydes and aqueous ammonia produces oil of symmetrical 5-acetyl-2,6-diaryl-4-ethoxy-5,6-dihydro-2H-1,3-thiazine derivatives (74)[26].



(73) (74)

Ar= -C_6H_5, p-CH_3O-C_6H_4, p-CH_3-C_6H_4, p-Br-C_6H_4

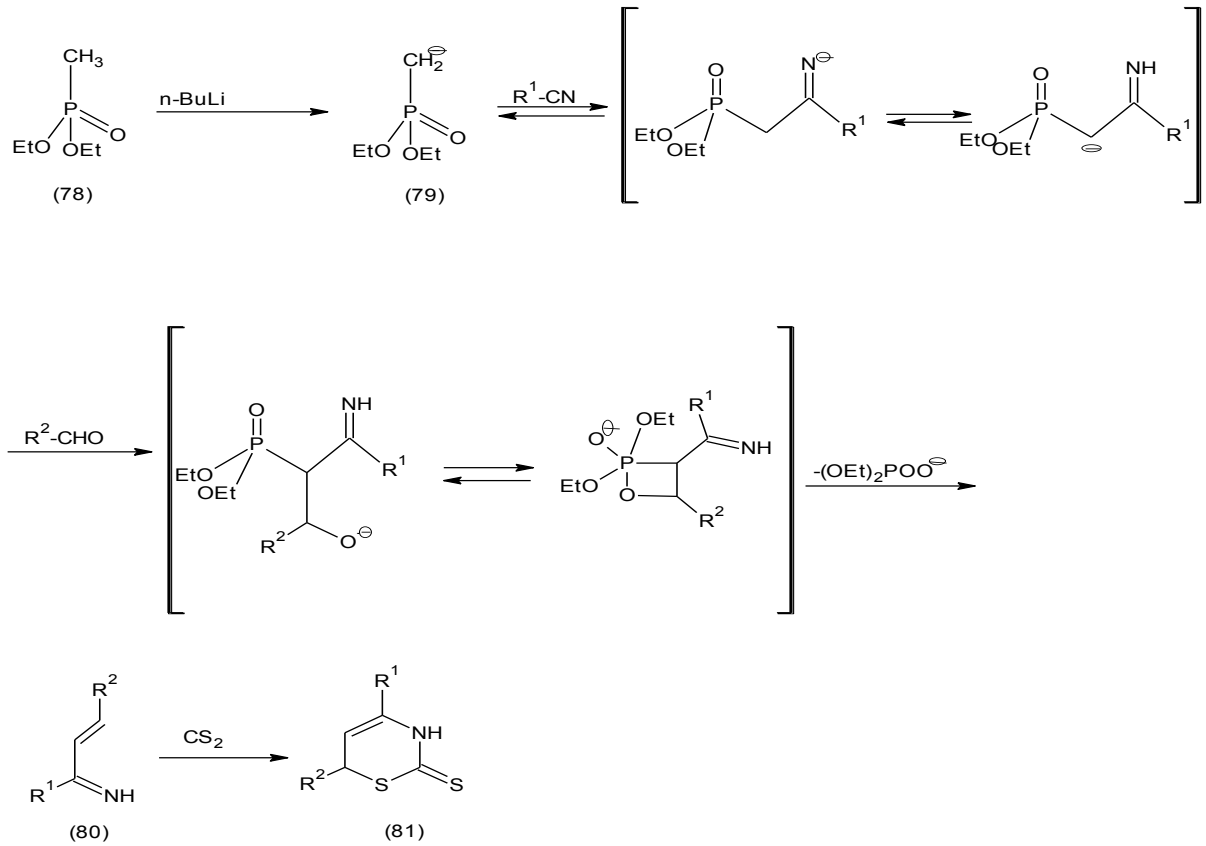
5. On heating 2,3-dihalopropylaminehydrohalide (75) with carbon disulfide produces mixture of 5-halo-3,4,5,6-tetrahydro-1,3-thiazine-2-thiones (76) and 5-halomethylthiazolidine-2-thiones (77). It has not been quite an efficient method as latter yields mixture of cyclic dithiocarbamates.[27]



(75) (76) (77)

X= -Cl, -Br

Diethyl methylphosphonate (78) on treating with n-butyllithium produces deprotonated diethyl methylphosphonate (79) which undergoes nucleophilic reaction with nitrile carbon of aryl nitrile followed by proton shift and subsequent Horner-Wadsworth-Emmons reaction with aldehyde to give 1-azadiene intermediate(80). The latter undergoes hetero Diels-Alder reaction with carbon disulphide to afford 3,6-dihydro-2H-1,3-thiazine-2-thiones (81) (scheme-5).[28]

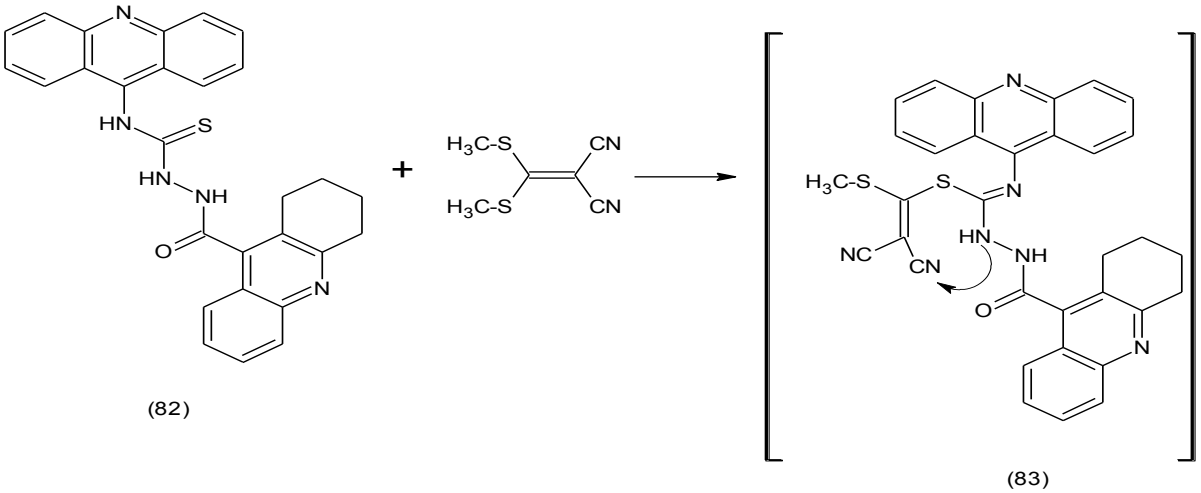


(78) (79) (80) (81)

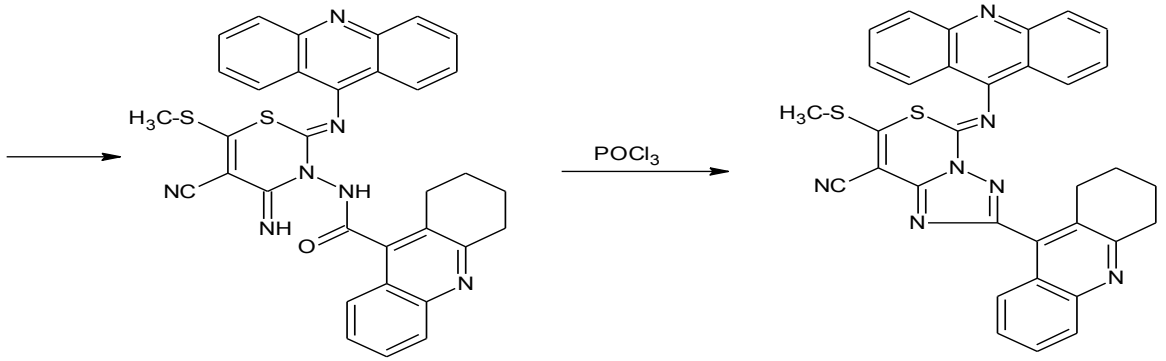
R^1, R^2= -C_6H_5, -iC_3H_7, 2, 6-$(CH_3)_2$-C_6H_3, p-F_3C-C_6H_4, p-CH_3O-C_6H_4, p-Br-C_6H_4, o-Br-C_6H_5

Scheme-5

6. 4-(Acridine-9-yl)-1-(1,2,3,4-tetrahydroacridine-9-ylcarbonyl) thiosemicarbazide (82) on refluxing with [bis(methylthio) methylene]malononitrile yields intermediate (83) which in situ by intramolecular cyclization of NH functional group with CN group produces N-[2-(9-acridinylimino)-5-cyano-4-imino-6-[methylthio)-2H-1,3-thiazin-3(4H)-yl]-1,2,3,4-tetrahyd-roacridine-9-carboxamide (84). The latter on treatment with $POCl_3$ gives 5-(9-acridinylimino)-7-(methylthio)-2-[1,2,3,4-tetrahydroacridine-9-yl)-[1,2,4] triazolo[1,5-c][1,3] thiazine-8-carbonitrile (85).[29]

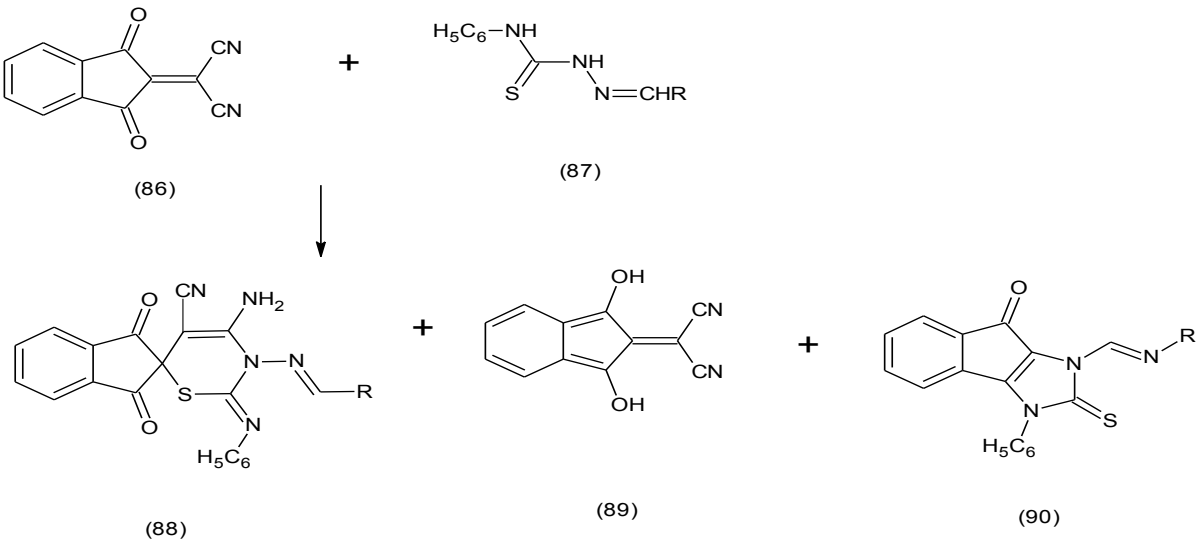


(82) (83)



(84) (85)

8. (2-Dicyanomethylidene)indan-1,3-dione (86) on stirring with (substituted) alkenylidene-hydrazinecarbothioamide (87) and their derivatives in ethylacetate produces dioxospiroindene[1,3] thiazine derivatives (88) along with byproducts (89-90).[30]

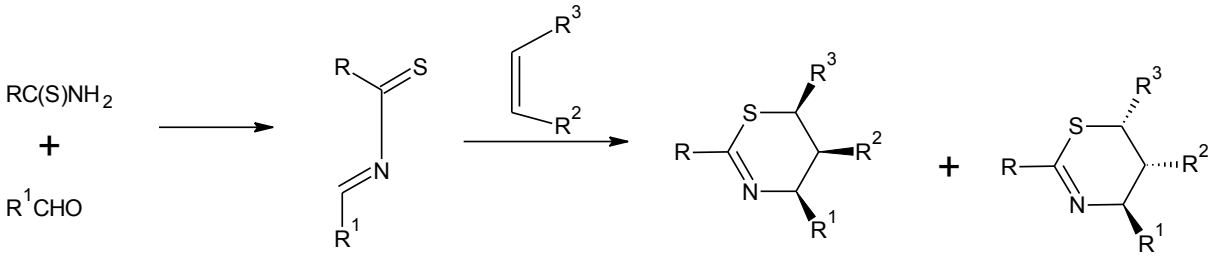


(86) (87)

(88) (89) (90)

R=C_6H_5-CH=CH, o-OCH_3-C_6H_4-CH=CH, CH_3-$(CH_2)_2$-CH=CH, CH_3-CH=CH, CH $(CH_3)_2$

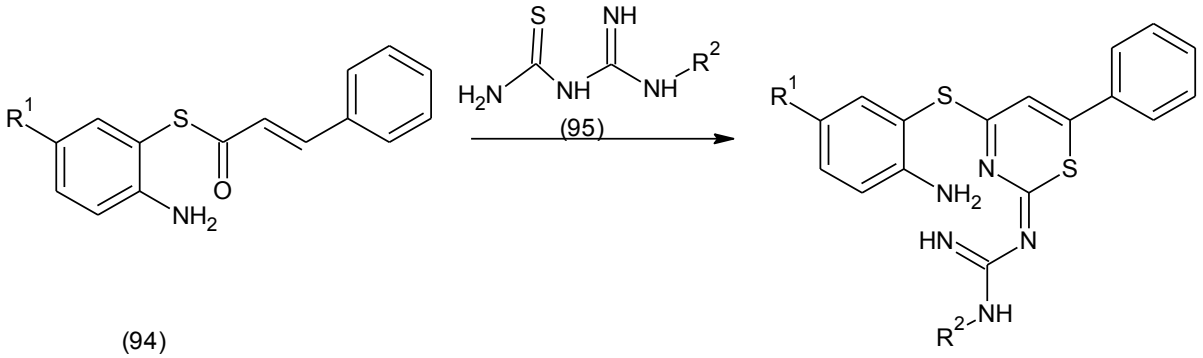
9. N-thioacyl imine heterodiene derivatives (91) procured from thioacetamide and aromatic aldehyde undergoes hetero Diels-Alder reaction with alkenes to give mixture of isomers of 1,3- thiazine derivative (92-93).[31]



(91) (92) (93)

R=-C_6H_5, -CH_3; R^1= -C_6H_5, p-Me-C_6H_4, p-Cl-C_6H_4, p-Br-C_6H_4, p-NO_2-C_6H_4, o-CH_3O-C_6H_4, m-HO-C_6H_4, m-Br-C_6H_4, m-NO_2-C_6H_4, 1-naphthyl, m-thienyl; R^2= -H, -$(CH_2)_4$, -$(CH_2)_6$, -$(CHCH_2)_2CH_2$; R^3= n-C_4H_9, -Ph, -$(CH_2)_2Br$, -$(CH_2)_2CO_2Et$, -$(CH_2)_2CO_2H$

10. 1-(2-Amino-5-substituted phenyl) mercapto-3-(substituted) phenyl-2-propen-1-one (94) from 2-amino thiophenol on refluxing with substituted amidinothiocarbamides (95) in basic medium for 4-5 hours produce 2-substituted guanidine-4-(2-amino-5-substituted phenyl)mercapto-6-phenyl-1,3-thiazines (96) and it has also been an efficient method for synthesizing 2-amino-4-(2-amino-5-substituted phenyl)mercapto-6-(substituted) phenyl pyrimidine derivatives.[32]

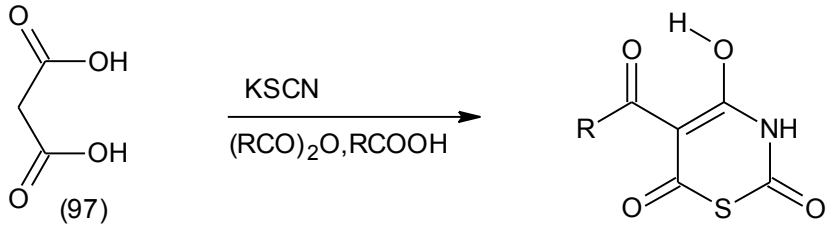


(94)

(96)

R^1= -H, -CH_3; R^2= -H, -C_6H_5, p-OCH_3-C_6H_4, p-Br-C_6H_4

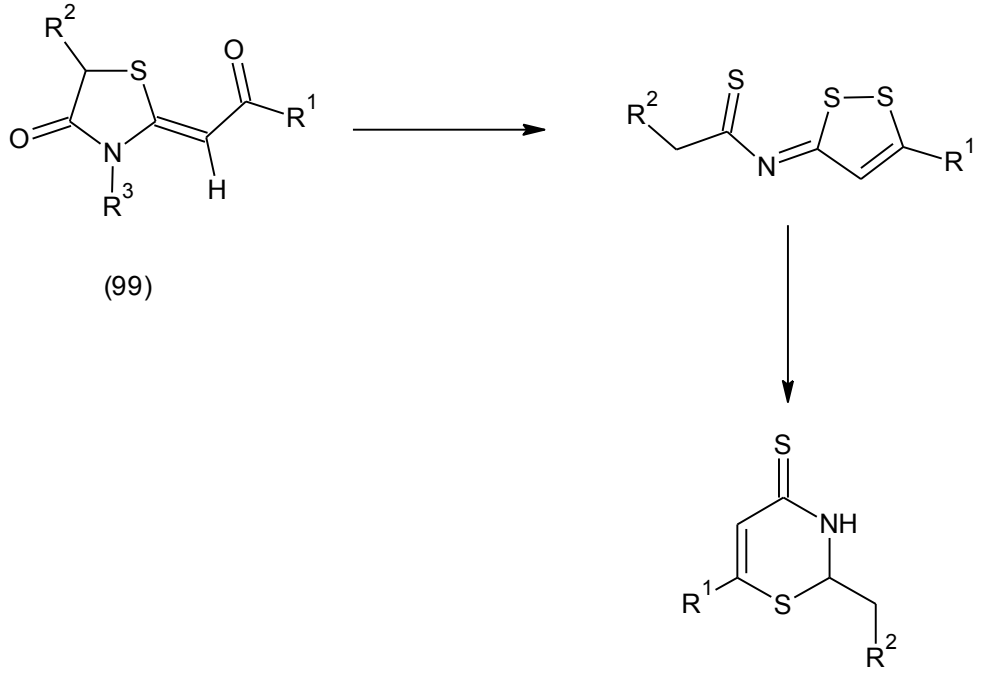
Malonic acid (97) reacts with potassium thiocyanate, acid anhydride in the presence of carboxylic acid to give 5-acyl-4-hydroxy-2H-1,3-thiazine-2,6(3H)-dione (98).[33]



(97) (98)

R= -CH_3, -C_2H_5, -C_3H_7

10. 1,2-Dithioles from 4-oxothiazolidines (99) when treated with sodium borohydride in ethanol produce 1,3 thiazine derivatives (100).[34]

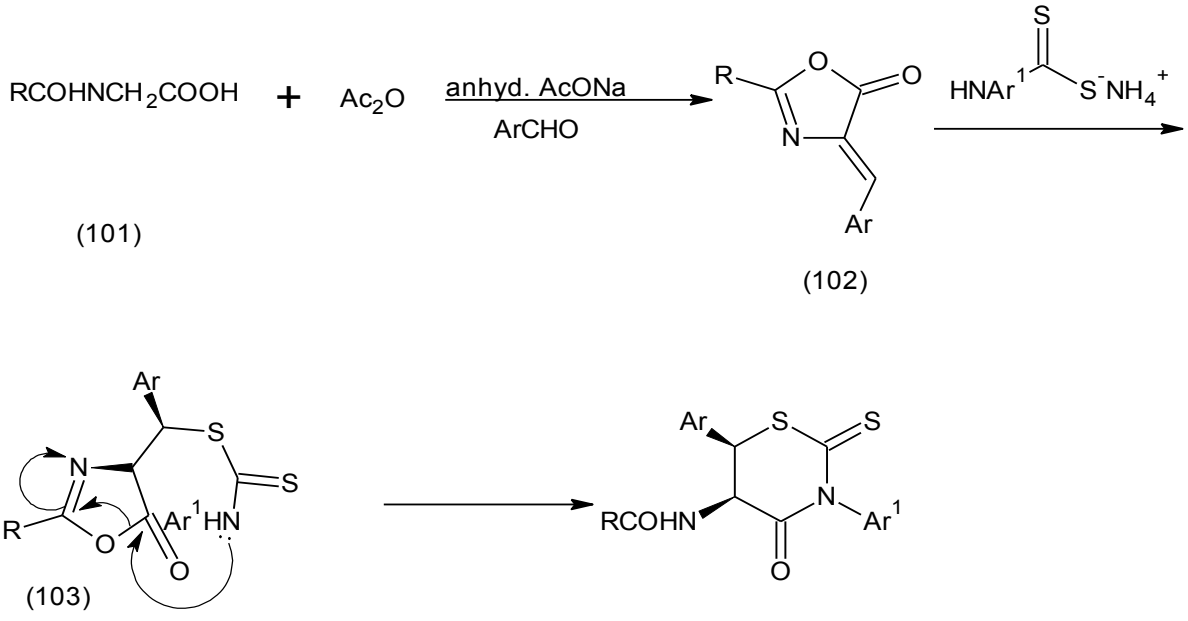


(99)

(100)

R^1= -COC_6H_5; R^2= -H, -CH_3, -$CH_2CO_2C_2H_5$

N-acylglycine (101) on treatment with anhydrous sodium acetate, acetic anhydride and arylaldehyde gives an intermediate azalactone (102). The latter undergoes Michael addition with N-aryldithiocarbamate in microwave to yield an adduct (103) in which the lone pair of nitrogen attacks the carbonyl carbon which by alternate cyclization produces 5-acylamino-3,6-diarylperhydro-2-thioxo-1,3-thiazine-4-one (104) (scheme-6).[35]



(101)

(102)

(103)

(104)

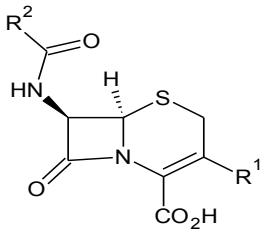
R= -C_6H_5, -CH_3; Ar= p-ClC_6H_4, p-$CH_3OC_6H_4$; Ar^1=-C_6H_5, o-$CH_3C_6H_4$, p-$CH_3OC_6H_4$

Scheme-6

BIOLOGICAL POTENTIAL OF 1, 3-THIAZINES

Antimicrobial Activity

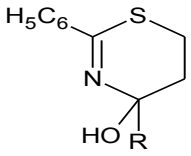
1,3-Thiazines and their derivatives have significant antimicrobial potential against various strains of bacteria, fungi etc.. The core moiety of 1,3-thiazines (C-N-S) forms an active site in antibiotics like Cephalosporins (105). 1,3-Thiazines derived from chalcones viz. 4-(2-hydroxy-3,5-dichlorophenyl)-6-(ethyl)-2-iminophenyl-3phenyl-1,3-thiazine (29), 4-(2-hydroxy-3,5-dichlorophenyl)-6-(ethyl)-2-iminophenyl-1,3-thiazine (28) etc. have also been evaluated for their in vitro antimicrobial activity against various gram positive- *Streptococcus aureus*, *S.subtilus* and gram negative bacteria- *E.coli* and *P.aeruginosa* [S.P.Rathod *et al.* (2010)].[15] Mamoru Koketsu *et al.*, 2002 synthesized series of 5,6-dihydro-4H-1,3-thiazine derivatives[36] (106) which showed antimicrobial activity against *M. tuberculosis H37Rv*. Tarik EL-Sayed Ali *et al.*, 2010 synthesized 1,3-thiazine derivatives having acridine ring (85) which besides showing antimicrobial activity against above mentioned species, also exhibit antibacterial activity against *Streptococcus pyogenes* and *Pseudomonas fluorescens* and *Pseudomonas phaseolicola* and antifungal activity against *Fusarium oxysporum* and *Aspergillus fumigates.*[29] Ramesh L. Sawant *et al.*, 2011 introduced electron donating groups like hydroxyl and methoxy group at the fourth position of phenyl rings in the series of 6-[4-substitutephenyl]-4-phenyl-6H-1,3-thiazine-2-amines (25) and N-[6-(4-substitutedphenyl)-4-phenyl-6H-1,3-thiazine-yl] acetamides (26) which enhances their antimicrobial activity[7]. Farooque Haider Zulfequar Haider, 2012 synthesized series of 4-(2-hydroxy-5-substitutedphenyl)-5-benzoyl-6-substitutedphenyl-2-imino-6H-2,3-dihydro-1,3-thiazine derivatives (22) which exhibits antimicrobial activity due to the presence of phenolic group. Its antibacterial activity has been observed to be enhanced by increasing the number of heteroatoms in the heterocyclic system.[6] Thanusu J *et al.*, 2010 introduced morpholine ring in the series of 4-(4-morpholinophenyl)-6-aryl-1,3-thiazin-2-amines (107) which showed substiantial antibacterial activity against *V.cholera* etc. and antifungal activity against various strains of fungi viz. *Rhizopus, M. gyseum*[37]etc.



R^1= -CH_3COOCH_3, -CH_3, -CH_3Cl

R^2= -CH_3CN, p-$(NH_2)C_6H_4$, p-$(OH)C_6H_4$

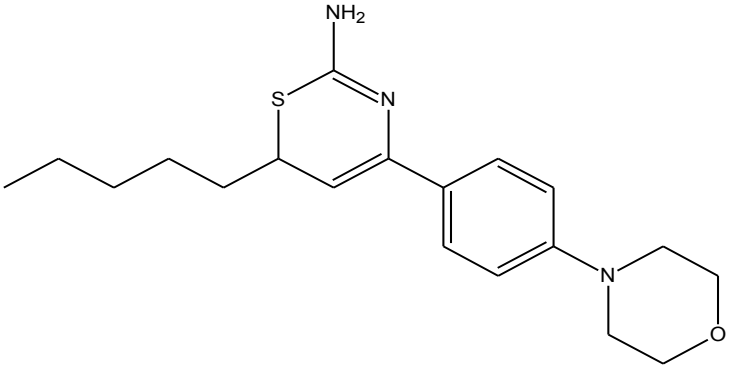
(105)



5, 6-dihydro-4H-1,3-thiazine derivative

R= -CH_3, -C_2H_5

(106)

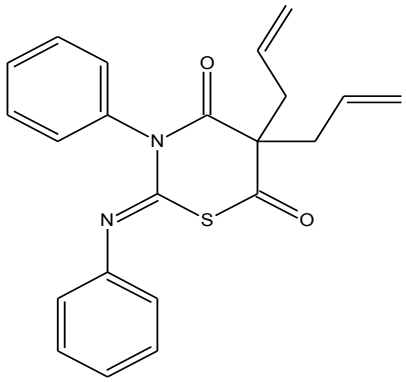


4-(4-morpholinophenyl)-6-amyl-1, 3-thiazine-2-amine

(107)

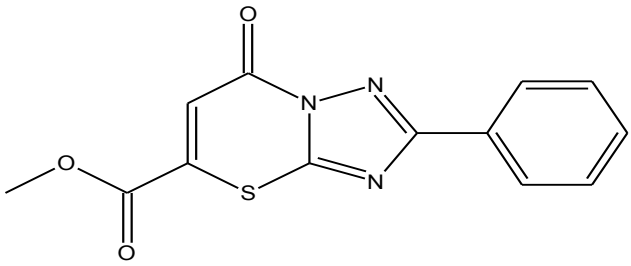
Other Activities of 1, 3-Thiazines

Li Fu *et al*., 2010 procured series of 6H-2-amino-4-aryl-6-(4-β-D-allopyranosyloxyphenyl)-1,3-thiazines (16) by Claisen Schmidst condensation which show strong calming activity in comparison with parent helicid.[4] T.P.Trofimova *et al*., 2008 gave a reaction scheme to synthesize 2-N-acylamino-5,6-dihydro-4H-1,3-thiazines (50) which showed excellent NOS inhibiting activity both in vivo and in vitro and also act as antihypotensive agents in vivo.[16] Kai H *et al.*, 2008 synthesized 2-arylimino-5,6-dihydro-4H-1,3-thiazines which show profound analgesic properties.[38] Tetrahydro-1,3-thiazines derivatives (108), tetrahydro [1, 3]-thiazine-4-one-6-carboxylic acid (109), tetrahydro [1,3]-thiazin-4,6-dione derivatives, 2-(2-amino-4-phenyl-6H-1,3-thiazin-6-yl)-4-[3-(2-amino-4-phenyl-6H-1,3-thiazine-6-yl) 4-hydroxy-benzyl]phenol and 2-[2-amino-4-(4-chlorophenyl)-6H-1,3-thiazin-6-yl]-4-hydroxybenzyl}phenol (56) etc. have also been known to exhibit strong anti-inflammatory activity and most of them are immunotropic in nature [Zawisza T *et al*., (1978&1981); R. Kalirajan *et al.* (2009), A. Nagaraj *et al.* (2008)].[9, 19, 39, 41] Derivatives of 1,2,4-triazolo [3, 2-b]-1,3-thiazine-7-ones (110) and amino/ guanidine thiazine derivatives (96) besides, possessing anti-inflammatory activity, also exhibits analgesic properties [Tozkoparan B et al. (2002); Vijay V. Dabholkar et al. (2011)].[32,40] The derivatives of 1H-pyrrolo [1, 2-c] [1,3] thiazine (66) have been reported to show moderate anticonvulsant activity [Tadeusz S. Jagodzinski *et al*., 2003].[23]



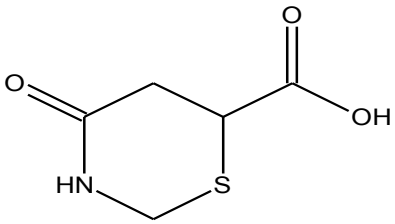
5,5-diallyl-2-phenylimino-3-phenyl-2,3,4,5-tetrahydro-[1, 3]-thiazine-4,6-dione

(108)



5-carbomethoxy-2-phenyl-7H-1,2,4-triazolo[3,2-b]-1, 3-thiazine-7-one

(109)

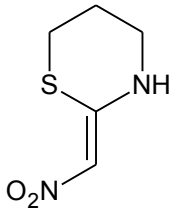


Tetrahydro[1, 3]-thiazine-4-one-6-carboxylic ac

(110)

Agrochemical Uses of 1,3-Thiazine Derivatives

Tetrahydro-2-(nitromethylene)-2H-1,3-thiazine (Nitromethylene) possess strong insecticidal properties (111)[Margulies, L et al. (1988)][42]. Perhydro dervivatives of 1,3-thiazine have obtained patent for their insecticidal properties against various nematodes[Jean-dominique bourzat et al. (1981)] [43].



(111)

Thus, variously substituted 1,3-thiazine derivatives procured largely through cyclo-condensations and few ring transformations have great synthetic utility, particularly for the synthesis of different heterocyclic systems. Besides having synthetic applications, these have also been remarkably known for their biological activities viz. pharmaceutical, agrochemical etc.

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Correspondence Author:
Cannoo Singh Damanjit
Department of Chemistry
Sant Longowal Institute of Engineering and Technology,
Longowal, Sangrur-148106,
Punjab, India.
Email: 13daman@gmail.com

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