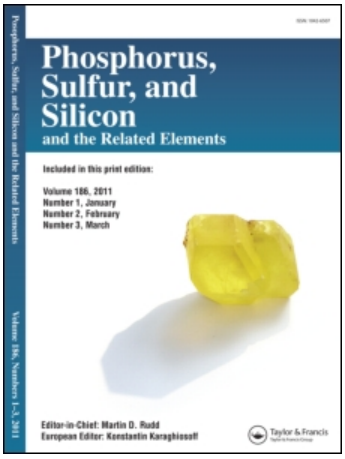

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Recent Trends in the Chemistry of Heterocyclic Sulfides, 1990-2000

M. S. K. Youssef[a]; R. A. Ahmed[a]
[a] Department of Chemistry, Assiut University, Assiut, Egypt

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Recent Trends in the Chemistry of Heterocyclic Sulfides, 1990–2000

M. S. K. Youssef
R. A. Ahmed
Department of Chemistry, Assiut University,
Assiut, Egypt

This review selectively describes work that generally reflects the recent current state of knowledge about heterocyclic sulfides while emphasizing important developments, methods of synthesis, main reactions, and their biological activities.

Keywords Arylheterocyclic sulfides; biological activity; diheterocyclic sulfides; sulfides; synthesis

Sulfides (RSR) are sulfur analogs of ethers, but there are some important differences between the chemistries of ethers and sulfides. Sulfur is more polarizable than oxygen, and sulfur compounds are more nucleophilic than their oxygen analogs. A second difference between sulfides and ethers is that sulfides are easily oxidized. The treatment of a sulfide with hydrogen peroxide at r.t. yields the corresponding sulfoxide (R_2SO), and further oxidation of the sulfoxide with a peroxy acid yields a sulfone (R_2SO_2).

SYNTHESIS OF SULFIDES

A variety of six- and five-membered heterocyclic rings have been reported to afford diheterocyclic and aryl heterocyclic sulfides on treatment with some reagents.

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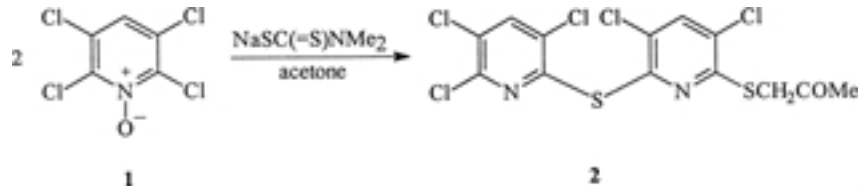
Address correspondence to M. S. K. Youssef, Assiut University, Department of Chemistry, Faculty of Science, Assiut 71516, Egypt. E-mail: salah_kamel2000@yahoo.com

1. Synthesis of Diheterocyclic Sulfides Containing (6-6) Heterocyclic Rings

a. From Pyridine Derivatives

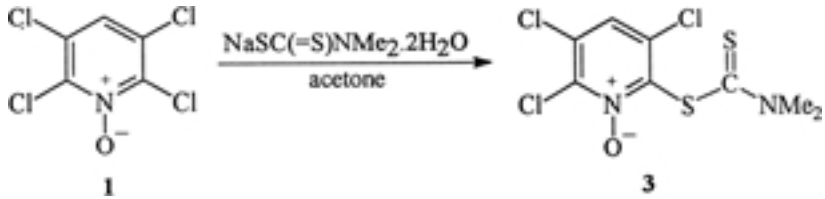
2,3,5,6-tetrachloropyridine-*N*-oxide **1** undergoes nucleophilic substitution reactions with sodium *N,N*-dimethyl dithiocarbamate (SDDC) at position 2 of the pyridine ring. Surprisingly, instead of the expected dialkyl dithiocarbamate derivative of **1**, 1-[6-(3′,5′,6′-trichloropyridine-2′-ylthio)-3,5-dichloropyrid-2-ylthio]propan-2-one (**2**) was obtained in boiling acetone.[1]



1 **2**

SCHEME 1

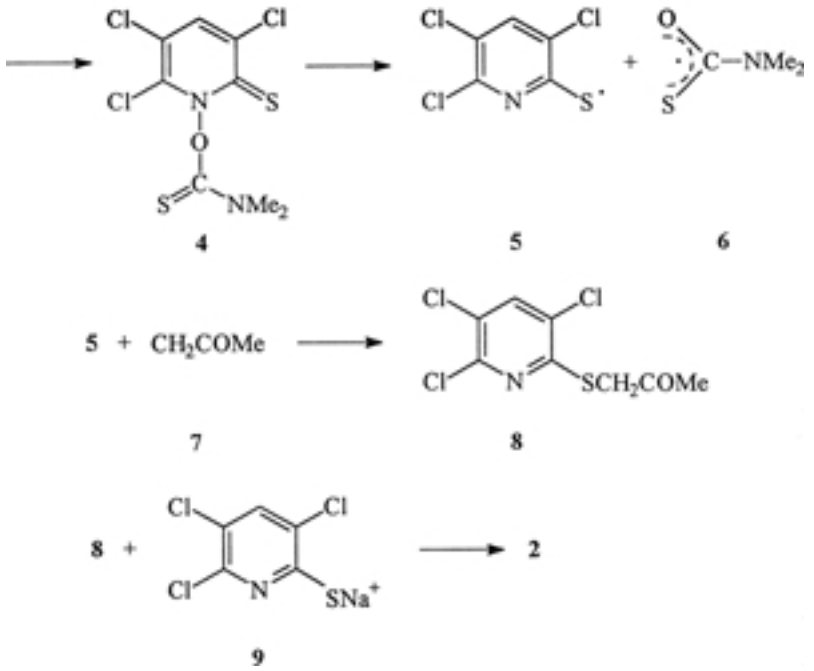
The formation of the dipyridyl sulfide fragment and the unusual introduction of an S-acetonyl group in position 2 of the pyridine ring can be explained by data on the radical decomposition of *o*-acyl derivatives of *N*-hydroxy-2-thiopyridones[2] and *o*-thiocarbamoyl oximes.[3] The reaction sequences probably proceed as follows. First, the substitution of **1** with a dithiocarbamate moiety gives intermediate **3**, which undergoes rearrangment to form a thermodynamically more stable product[2] **4**. Upon heating, compound **4** breaks down to the radical pair **5** and **6**, and their reactivities determine further conversion pathways. Radical **5** reacts with radical CH_2COMe **7** (which can be formed from radical **5** or **6** with acetone) to produce intermediate **8**. Then the chlorine atom at position 6 in the pyridine ring of **8** can be substituted with trichloropyridine thiolate anion **9** yielding the final product **2**.



1 **3**

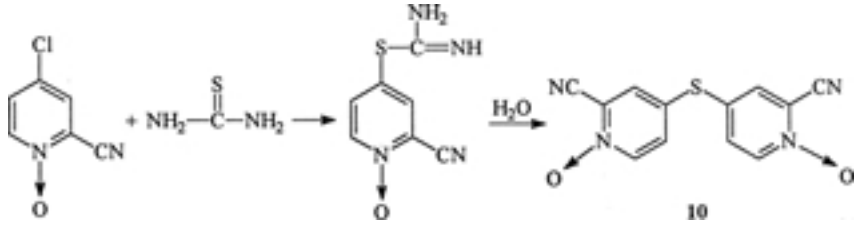
SCHEME 2

The formation of intermediate 9 probably takes place by the radical stabilization of **5** in the reaction medium.



SCHEME 3

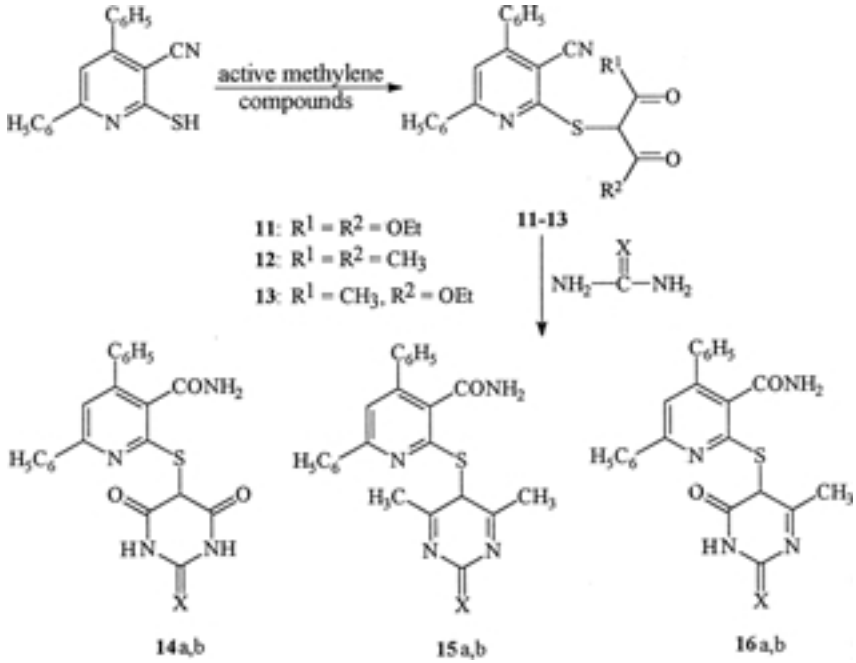
Treatment of 4-chloropicolinonitrile-1-oxide with thiourea gave an intermediate isothiuronium salt, which was hydrolyzed to give 4,4-thio bis[2-cyanopyridine-1-oxide] **10**.[4]



SCHEME 4

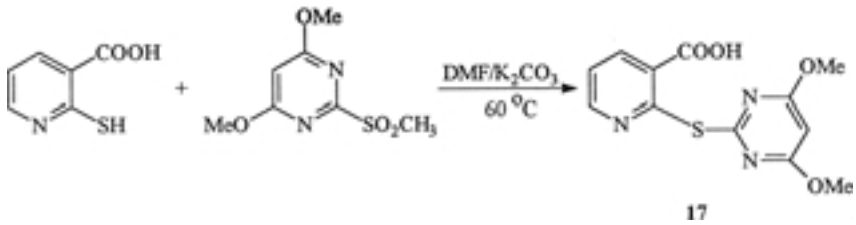
The reaction of 3-cyano-4,6-diphenylpyridine-2-thione with active methylene compounds such as diethyl malonate, acetylacetone, and ethyl acetoacetate in absolute ethanol using fused sodium acetate[5] afforded compounds **11–13**, respectively. The latter reacted with urea or thiourea to give the corresponding 3-carboxamido-4,6-diphenyl-2-[4,6-dioxo-2-oxo(thioxo)pyrimidinylthio **14**a,b, 4,6-dimethyl-2-oxo(thioxo)-

pyrimidinylthio **15**a,b and 4-methyl-6-oxo-2-oxo(thioxo)-pyrimidinylthio pyridines **16**a,b, respectively.



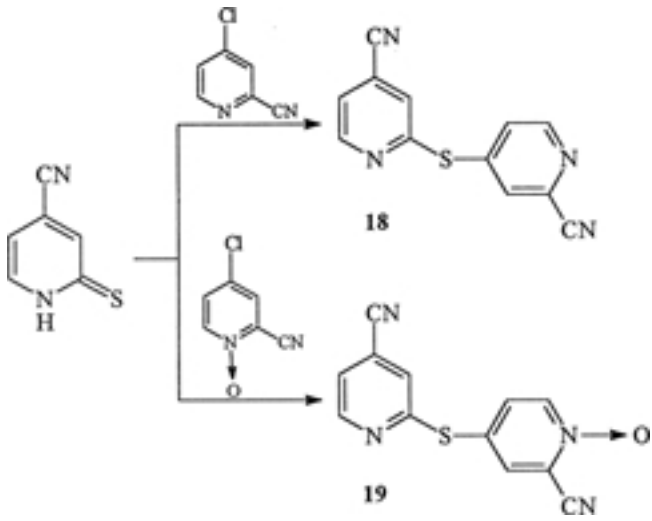
SCHEME 5

The reaction of 2-mercaptonicotinic acid with 4,6-dimethoxy-2-methyl-sulfonylpyrimidine in DMF in the presence of K_2CO_3 gave 2-pyrimidinylthio-3-carboxypyridine (**17**).[6]



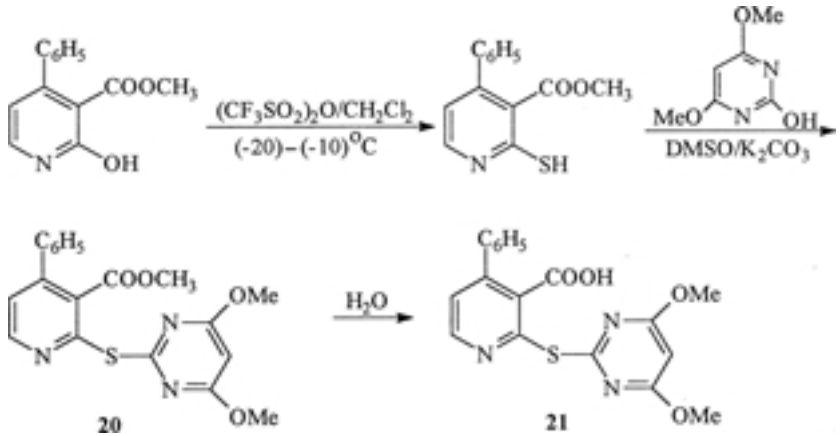
SCHEME 6

Unsymmetrical dipyridyl sulfides[7] **18** and **19** were prepared by the substitution of thioxopyridine carbonitrile with appropriate chloropyridine carbonitrile and their oxides.



SCHEME 7

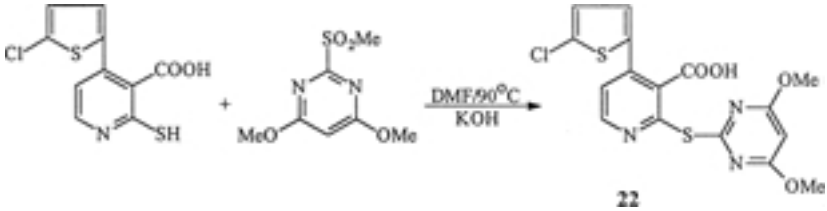
The formation of pyridylthiopyrimidine[8] derivative **20** by the sulfonylation of methyl 2-hydroxy-4-phenylnicotinate with $(CF_3SO_2)_2O$ in methylene chloride at −20 to −10°C, followed by condensation with 4,6-dimethoxy-2-hydroxypyrimidine in DMSO in the presence of K_2CO_3, gave the product **20**, which hydrolyzed to the corresponding acid **21**.



SCHEME 8

The reaction of 2-mercapto-4-(5-chloro-2-thienyl)nicotinic acid [prepared from 2-bromo-4-(5-chloro-2-thienyl)nicotinic acid with thiourea] with 4,5-dimethoxy-2-methylsulfonylpyrimidine in DMF and H_2O in

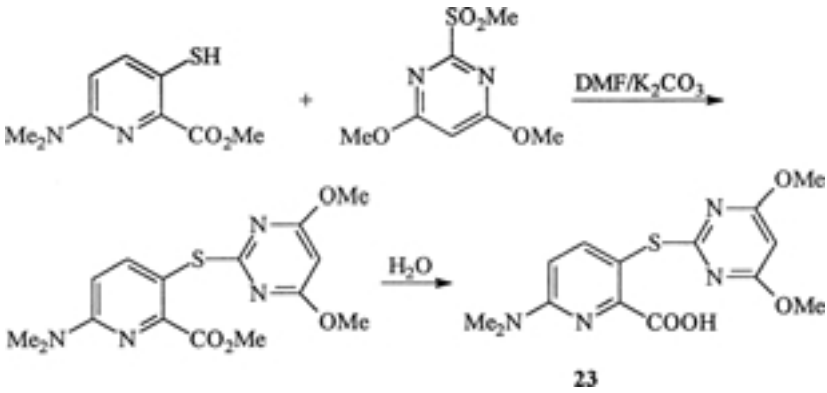
the presence of KOH gave, after acidification with 10% HCl, 4-(5-chloro-2-thienyl)-2-(4,6-dimethoxypyrimidin-2-ylthio)nicotinic acid (**22**).[9]



22

SCHEME 9

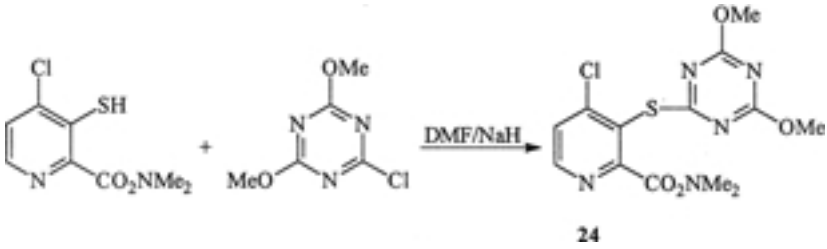
The (pyrimidinylthio)picolinic acid[10,11] **23** was prepared by the reaction of methyl 6-(dimethylamino)-3-mercaptopicolinate with 4,6-dimethoxy-2-methyl-sulfonylpyrimidine in DMF in the presence of K_2CO_3, and the resulting product was hydrolyzed to give **23**.



23

SCHEME 10

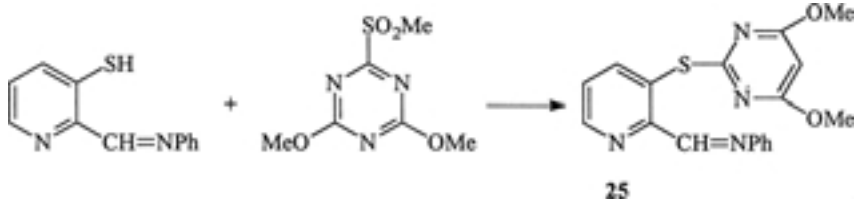
When 3,2-Cl(Me_2NO_2C)C_5H_2N-SH was treated with 4,6-dimethoxy-2-chloro-1,3,5-triazine in DMF in the presence of sodium hydride, the pyridinyl-thiotriazine derivative **24**[12] was obtained.



24

SCHEME 11

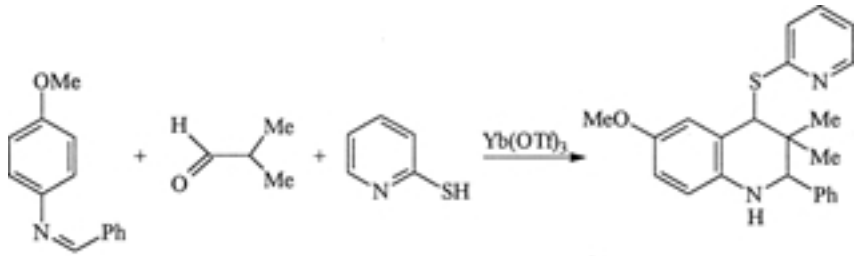
The synthesis of 2-methylidene aniline-3-(4,6-dimethoxy-2-pyrimidinylthio)-pyridine (**25**) was carried by the condensation of 2-HS-(C_5H_3N)CH=NPh with 4,6-dimethoxy-2-pyrimidinymethyl sulfone.[13]



25

SCHEME 12

The Lewis-acid promoted reaction of *N*-arylimines with alkenes[14] and dienes[15–17] represents a simple and mild procedure for the synthesis of 1,2,3,4-tetrahydroquinolines (THQ),[18] by multicomponent synthesis in which an imine (Ar—N=CHR) (pre-formed or generated in situ) reacts with an α-branched and enolizable aldehyde (R^1R^2CHCHO) and a third reagent likely acting as a nucleophile (ROH, $ArSH$, $ArNH_2$, or H_2O) under $Yb(OTf)_3$ ($OTf = OSO_2CF_3$) catalysis. Thus, 2-phenyl-3,3-dimethyl-4-(2′-pyridylthio)-6-methoxy-1,2,3,4-tetrahydroquinoline (THQ)[19] (**28**) was synthesized by the reaction of imine **26**, aldehyde **27**, and 2-pyridylthiol at r.t. in CH_2Cl_2 and in the presence of $Yb(OTf)_3$.

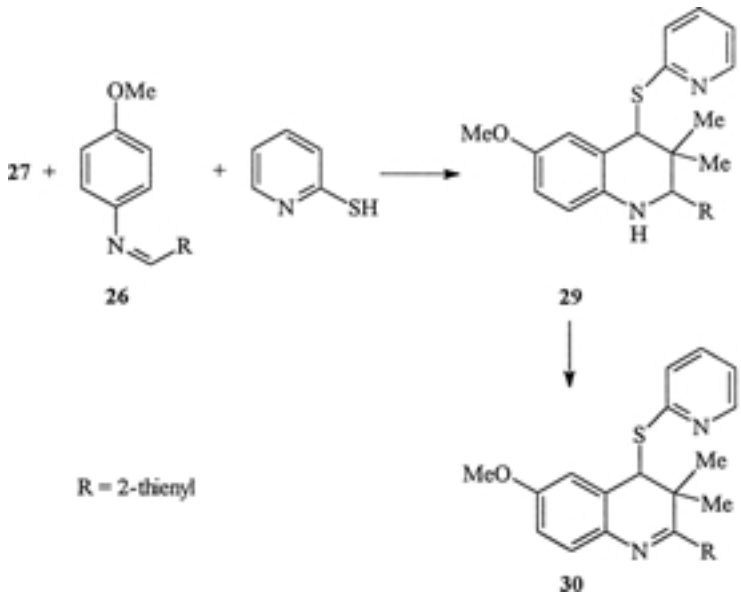


26 **27** **28**

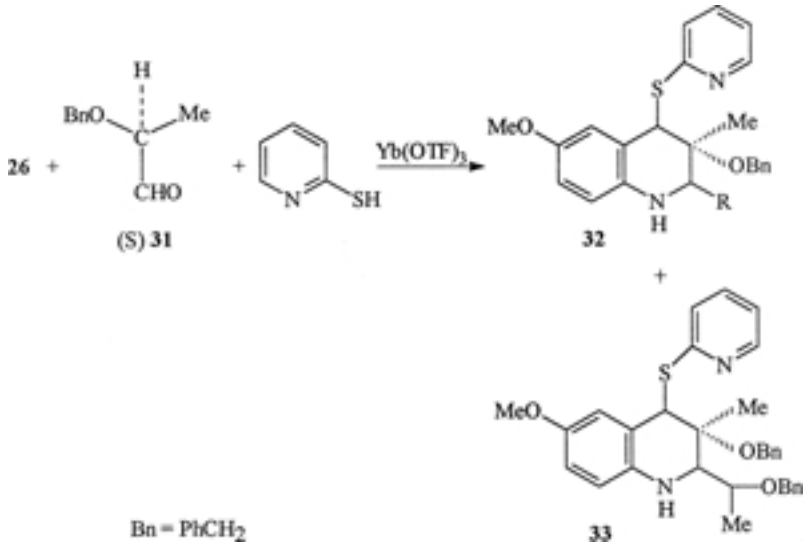
SCHEME 13

However, the reaction of imine 26 derived from 2-thienylcarbaldehyde with aldehyde **27** and 2-pyridylthiol gave 3,4-dihydroquinoline **30** obtained from the initially produced THQ **29**.

The reaction of (S)-aldehyde **31** with imine **26** in the presence of $Yb(OTf)_3$ in CD_2Cl_2 at r.t. gave THQ **32** and **33.** THQ synthesis in situ generation of the imine component was attempted when a mixture of 4-methoxyaniline, cyclohexane carboxyaldehyde, 2-mercaptopyridine, and $Yb(OTF)_3$ in CH_2Cl_2 was stirred at r.t. Finally the synthesis of

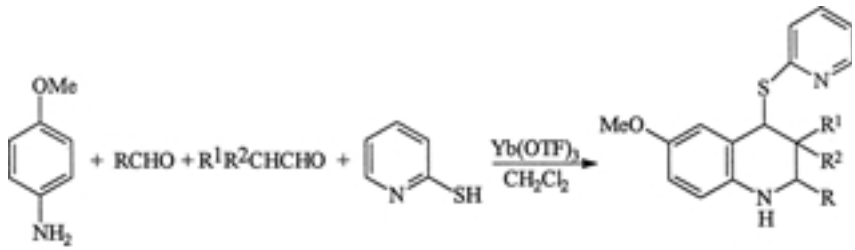


SCHEME 14



SCHEME 15

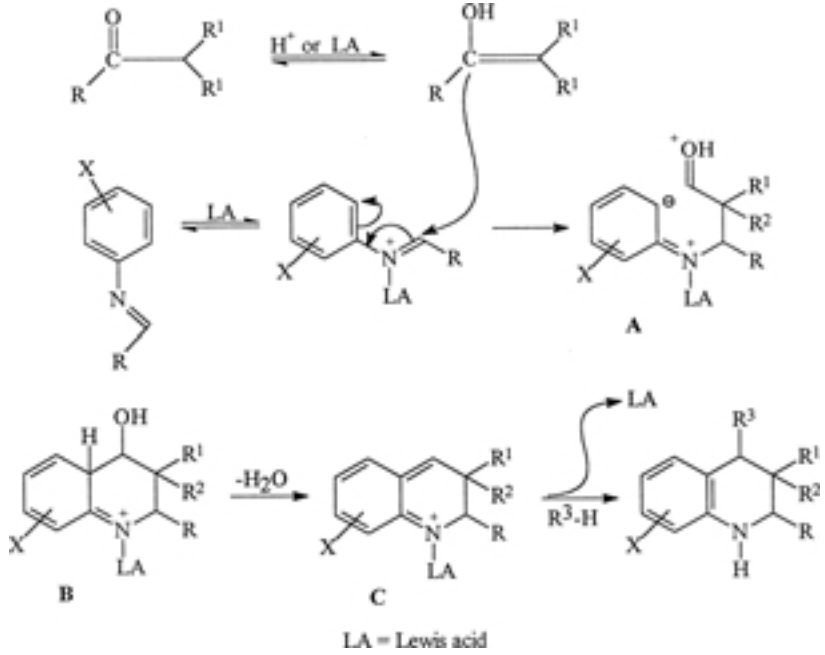
THQ **34** was also achieved by the four component reaction[19] of 4-methoxyaniline, benzaldehyde, 2-methyl propanal, and 2-pyridylthiol under the $Yb(OTf)_3$ catalyst.



R = C_6H_{11}; R^1R^2 = -$(CH_2)_5$-
R = Ph; R^1 = Me; R^2 = Ph

SCHEME 16

The possible mechanism[19] of a new multicomponent synthesis of THQ by a $Yb(OTf)_3$-catalyzed reaction of an imine, an aldehyde, and a nucleophile can be represents as follows (Scheme 17):

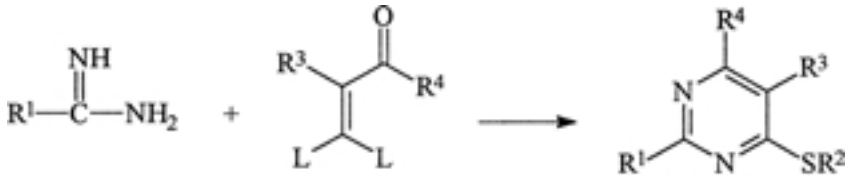


SCHEME 17

The enol form of the aldehyde (obtained either by $Yb(OTf)_3$ or by TfOH promoted enolization) should react with the imine activated by $Yb(OTf)_3$ (or TfOH) to afford adduct **B**, possibly via intermediate **A**, upon water elimination and **B** gives **C**, The addition of R^3 -H, acting as a nucleophile, leads to rearomatization, formation of THQ, and catalyst release.

b. From Pyrimidine Derivatives

Substituted pyrimidine derivatives **35** were synthesized by reacting an amidine R^1-C(=NH)NH_2 or its salt with 3,3-disubstituted vinylcarbonyl compound.[20]



35

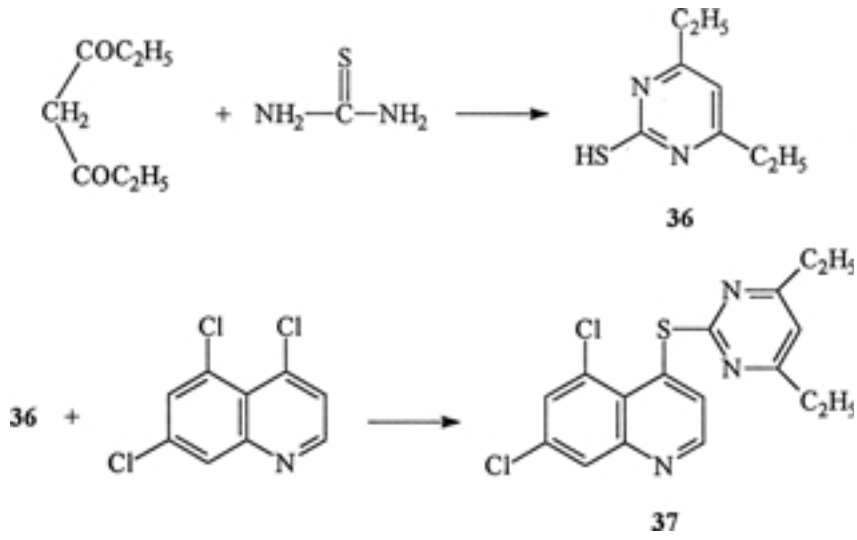
R^1, R^2 = heteroaryl, Ph
R^3, R^4 = H, (un) substituted alkyl, Ph
L = halo, SR^2
(a) in an inert solvent, in the presence of a base, and a compound HSR^2 in the event that L = halo.
(b) in an inert solvent and in the presence of a base in the event that L = SR^2.

SCHEME 18

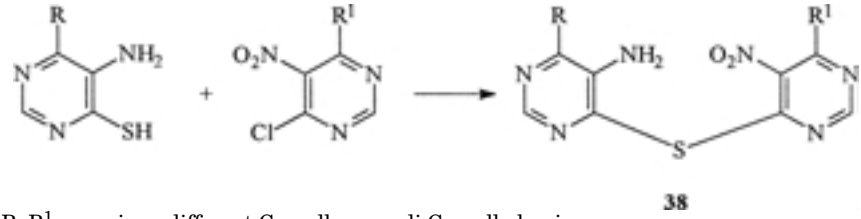
Pyrimidinylthioquinoline **37** was synthesized by the reaction of 2-mercaptopyrimidine with 4-chloroquinoline in molten states or in an inert solvent.[21] A mixture of thiourea, 3,5-heptanedione, and hydrochloric acid in ethanol was refluxed to give pyrimidine derivative **36**, the HCl salt of which was treated with 4,5,7-trichloroquinoline in *N,N*-dimethylimidazolidinone at r.t. to give the sulfide **37**.

Also, the reaction of aminomercaptopyrimidines with chloronitropyrimidines in an organic solvent in the presence of a base gave dipyrimidinyl sulfides **38**.[22]

Other derivatives of pyrimidinylthioquinoline **41** were synthesized by the following reactions: (i) mercaptoquinoline derivatives with chloropyrimidine[23] derivatives or (ii) chloroquinoline derivatives with mercaptopyrimidine[24] derivatives in the presence of a base in an inert solvent. Mercaptoquinolines or chloroquinoline derivatives **39** were dissolved in 1,3-dimethylimidazolidinone followed by the addition of sodium hydride, and, after stirring at r.t. chloropyrimidine or



SCHEME 19



R, R^1 = equiv or different $C_{1\text{-}4}$ alkoxy or di $C_{1\text{-}4}$ alkylamino

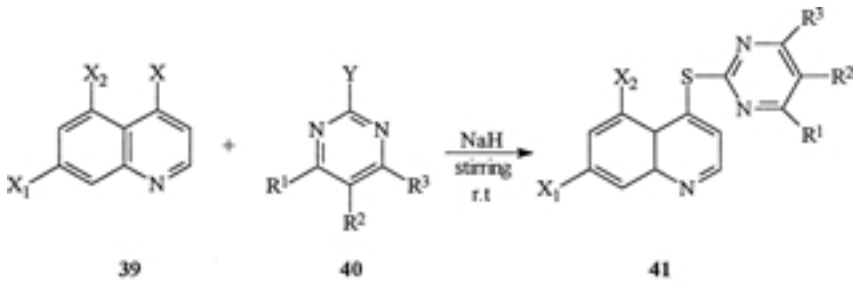
SCHEME 20

mercaptopyrimidine derivatives **40** were added at 25°C to give the target sulfides **41**.

c. From Thioquinanthrene Derivatives

The functionalization of quinoline in the 3- and 4-positions can be efficiently carried out by the reaction of thioquinanthrene **42** with sodium alkoxides;[25,26a,27] these reactions are performed in dimethyl formamide or dimethyl sulfoxide at 70°C, run by the cleavage of one 4-quinolinyl sulfur bond in the 1,4-dithiin ring of **42** to form sodium-4-(4-alkoxy-3-quinolinylthio)-3-quinolinyl-thiolates as the primary product. The latter was alkylated directly in an aqueous solution of alkyl halides to 4-methoxy-3′-methylthio-3,4′-quinolinyl sulfides **43**.[25,28]

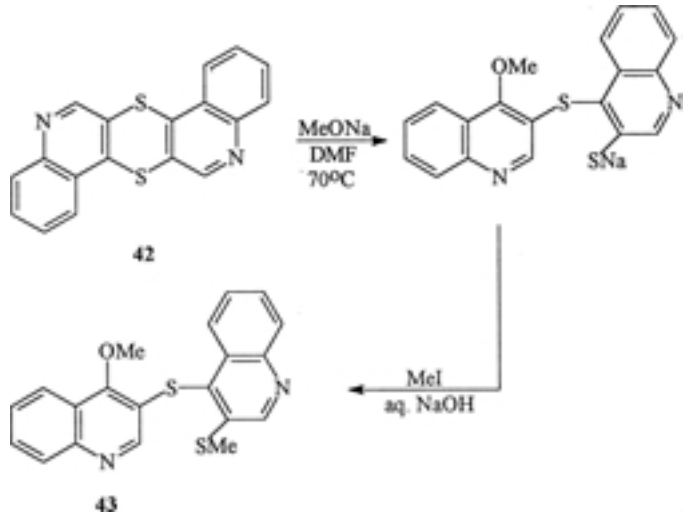
Also, the reaction of thioquinanthrene **42** with *6M* excess KOMe[29] gave the dipotassium salt of the (quinolinylthio)quinolinethiol **44**,



39 40 41

X = SH, Cl; X_1 = H, Cl; X_2 = Cl, I
Y = SH, Cl; R_1, R_3 = H, OMe, SMe; R_2 = H, Me

SCHEME 21



42 43

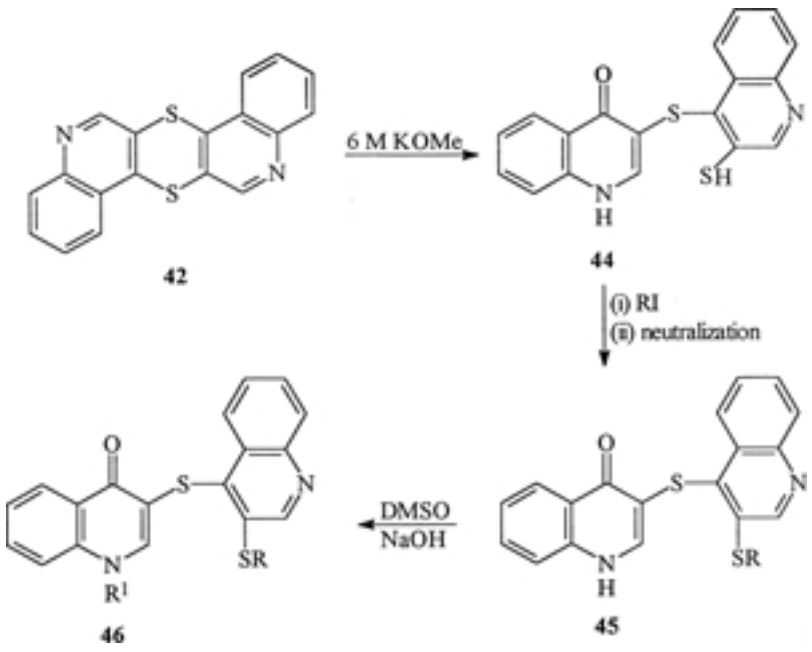
SCHEME 22

which underwent alkylation and neutralization to give the diquinolinyl sulfides **45.** Alkylation of the latter in DMSO/aqueous alkaline solution gave the dialkyl diquinolinyl sulfides **46**.

The reaction of thioquinanthrene[26a] **42** with sodium alkoxides, followed by S-alkylation, gave 4-alkoxy-3′-(alkylthio)-3,4′-diquinolinyl sulfides **43** and, in some cases, 1,4-dihydro-4-oxo-3′-(methylthio)-3,4′-diquinolinyl sulfide **45**.

d. From Quinazolone Derivatives

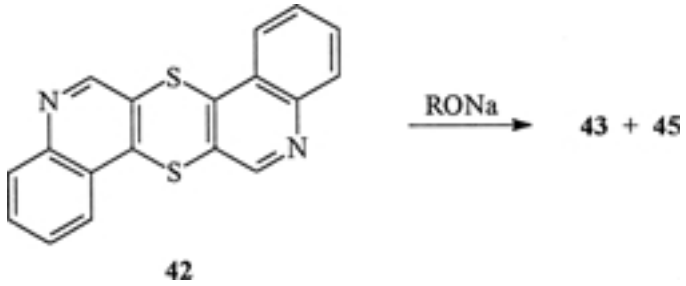
The cyclization of 2-(3-phenylthioureido)benzoic acid in concentrated sulfuric acid at r.t.[30] gave 3-phenyl-2-thioxo-4-quinazolone, which



R = R^1 = Me, Et, Pr
R, R^1 = Me, Bu, Me, Et, Me, Et

R = Me, Et, Pr, benzyl

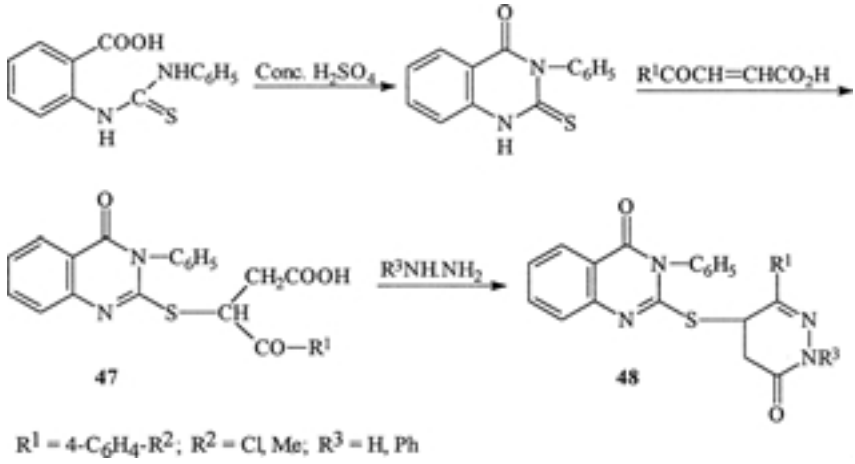
SCHEME 23



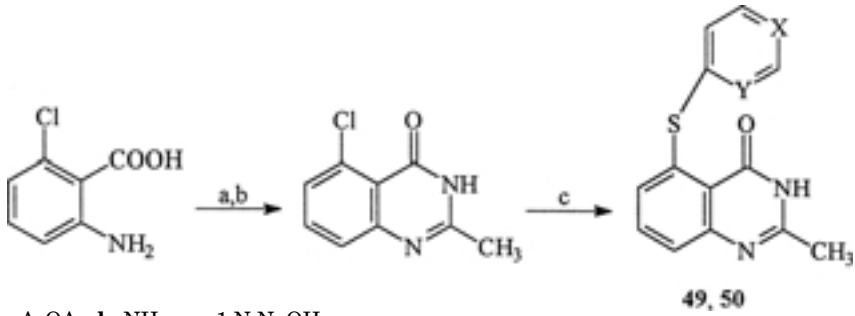
SCHEME 24

reacted as a thiol with activated olefinic compounds to yield the *Michael* adducts **47**. Condensation of the latter with hydrazine yielded the pyridazinone derivatives **48**.

The starting material for the synthesis of 2-methyl-5-(pyridin-4-ylsulfanyl)-3*H*-quinazolin-4-one **49** or methyl-5-(pyridin-2-ylsulfanyl)-3*H*-quinazolone-4-one[31] **50** was 5-chloro-2-methyl-3*H*-quinazolin-4-one (obtained from anthranilic acid derivatives). The latter was treated with



SCHEME 25

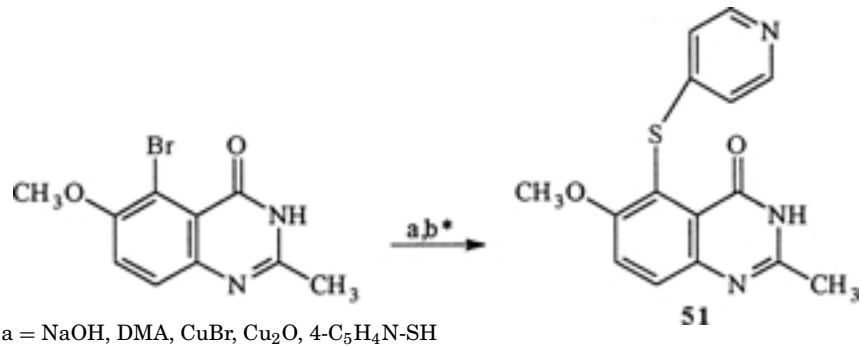


a: AcOAc, **b**: NH_3, aq. 1 N NaOH;
c: NaH, DMA, CuBr, Cu_2O + 4-(HS)C_5H_4N and or 2-(HS)C_5H_4N
49: X = N; Y = CH, **50**: X = CH, Y = N

SCHEME 26

4-mercaptopyridine or 2-mercaptopyridine in presence of DMA, NaH, CuBr, and Cu_2O.

6-methoxy-2-methyl-5-(pyridin-4-ylsulfanyl)-3*H*-quinazolin-4-one (**51**) was obtained from 5-bromo-6-methyoxy-2-methyl-3*H*-quinazolin-4-one[31] in DMA with 4-mercaptopyridine in the presence of NaOH, DMA, CuBr, and Cu_2O. The synthetic strategy was based on the displacement of a halogen at the 5-position of a quinazoline by various aryl thioanions.

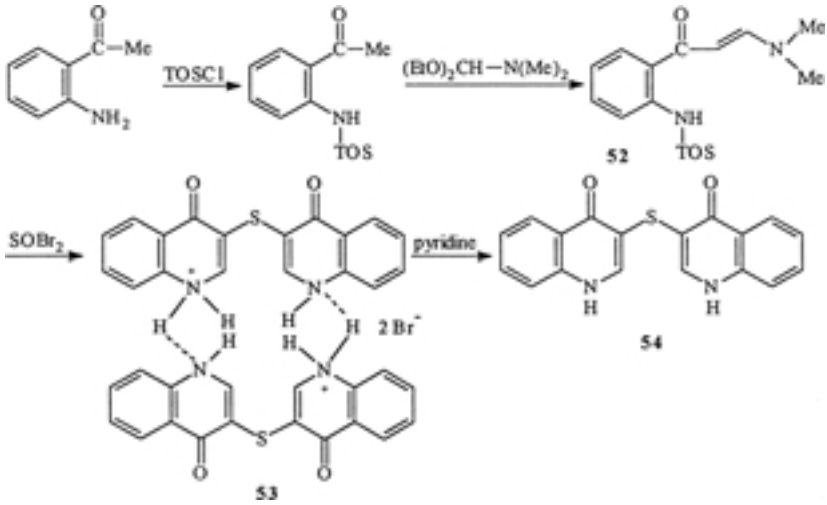


a = NaOH, DMA, CuBr, Cu_2O, 4-C_5H_4N-SH
b* = HBr, AcOH

SCHEME 27

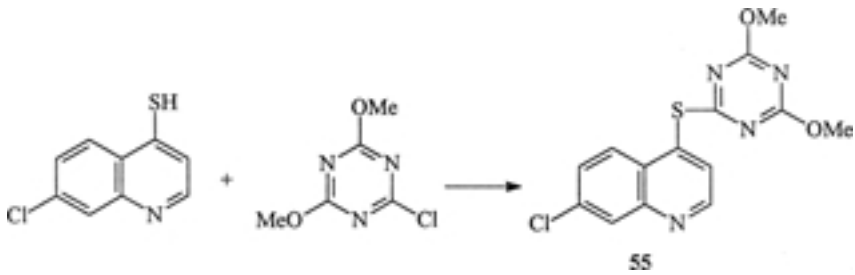
e. Miscellaneous Syntheses

To prepare a sulfur-bridged bis-quinolone derivative **54**, the tosylated enaminone **52** (prepared from the reaction of 2-tosylaminophenyl-l-ethan-l-one with *N*,*N*-dimethylformamide diethylacetal) reacted with thionyl bromide to give 3,3′-thio-bis-(1,4-dihydroquinolin-4-one)hydrobromide **53**, which cyclized in pyridine giving 3,3′-thio-bis-(1,4-dihydroquinolin-4-one) (**54**).[32]



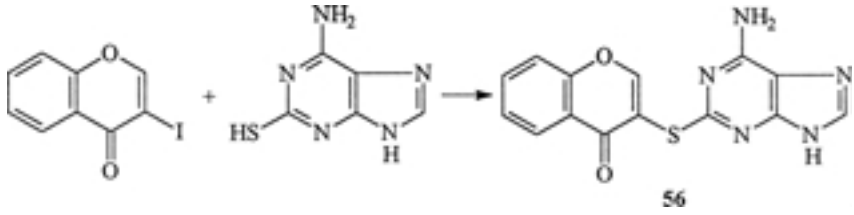
SCHEME 28

Triazinylthioquinoline[33] **55** was synthesized by the reaction of 7-chloro-4-mercaptoquinoline with 4,6-dimethoxy-2-chlorotriazine in the presence of 1,3-dimethyl-2-imidazolidinone.



SCHEME 29

Also, the reaction of 3-iodo-4*H*-l-benzopyran-4-one with 2-thiocytosine gave the corresponding sulfide **56**.[34]

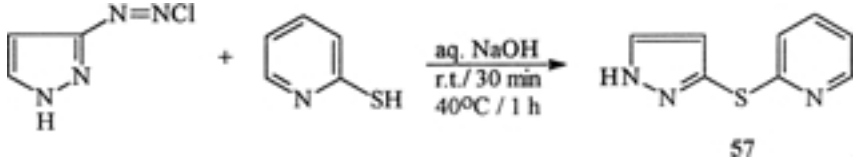


SCHEME 30

2. The Synthesis of Diheterocyclic Sulfides Containing (6-5) Heterocyclic Rings

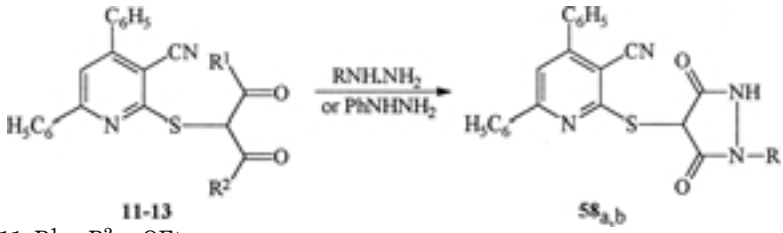
a. From Pyridine Derivatives

The reaction of pyridine-2-thiol with a diazonium compound (obtained by treatment of 3-aminopyrazole with nitrite[35] in the presence of an acid) with NaOH in H_2O gave 3-(2-pyridylthio)pyrazole (**57**).



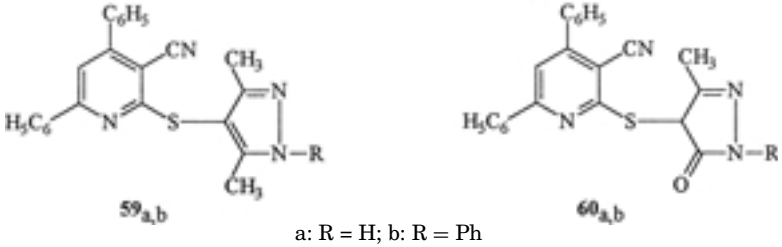
SCHEME 31

The condensation of compounds **11–13** with hydrazine hydrate or phenyl hydrazine[5] gave 3-cyano-4,6-diphenyl-2-[3,5-dioxopyrazolinylthio **58**$_{a,b}$, 3,5-dimethylpyrazolinylthio **59**$_{a,b}$, and 3-methyl-5-oxopyrazolinylthio]pyridine **60**$_{a,b}$, respectively. Also, the interaction of compounds **11–13** with hydroxylamine hydrochloride[5]



11-13 **58a,b**

11: $R^1 = R^2 = OEt$
12: $R^1 = R^2 = CH_3$
13: $R^1 = CH_3$; $R^2 = OEt$

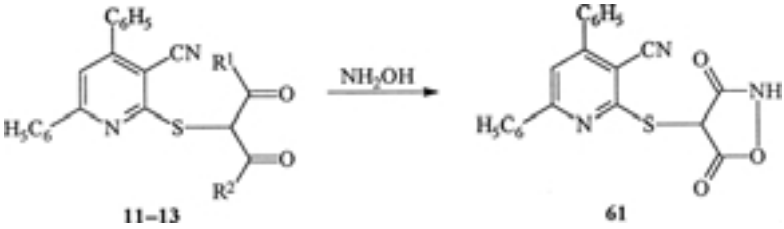


59a,b **60a,b**

a: R = H; b: R = Ph

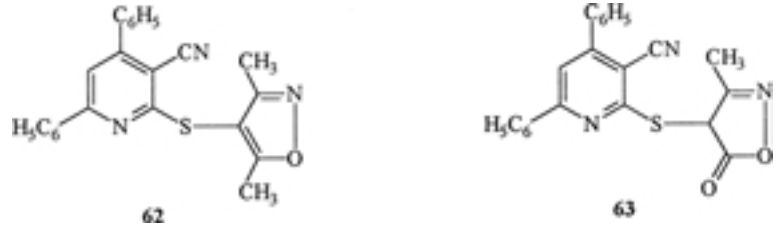
SCHEME 31a

afforded 3-cyano-4,6-diphenyl-2-[3,5-dioxoisoxazolinylthio **61**, 3,5-dimethylisoxazolinylthio **62**, and 3-methyl-5-oxo-isoxazolinylthio]-pyridines **63**, respectively.



11–13 **61**

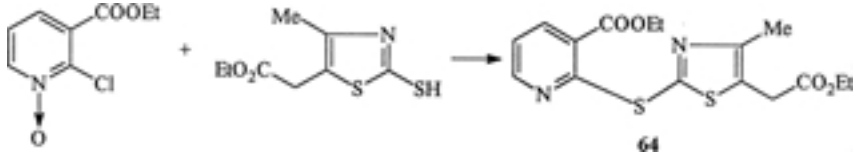
11: $R^1 = R^2 = OEt$
12: $R^1 = R^2 = CH_3$
13: $R^1 = CH_3$; $R^2 = OEt$



62 **63**

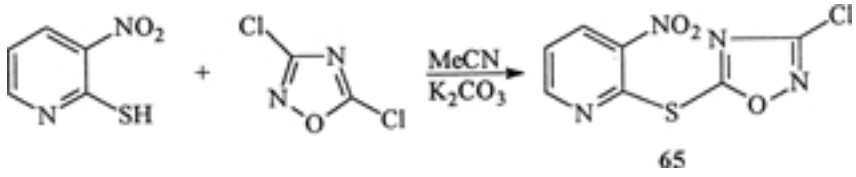
SCHEME 32

The substitution of ethyl 2-chloro-3-pyridine carboxylate-1-oxide with ethyl-2-mercapto-4-methylthiazole-5-acetate[36] followed by the reduction of the *N*-oxide with PCl_3 afforded **64**.

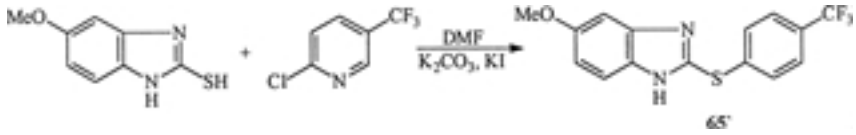


SCHEME 33

5-(pyridylthio)-3-chloro-1,2,4-oxadiazole **65** as a microbicide[37] was synthesized by the interaction of 3-nitro-2-mercaptopyridine with 3,5-dichloro-1,2,4-oxadiazole in acetonitrile containing K_2CO_3. Also, the reaction of a mercaptobenzimidazole[38] derivative in a solution of DMF containing K_2CO_3 and KI with chloropyridine derivative gave pyridinyl-thiobenzimidazole **65**.



SCHEME 34

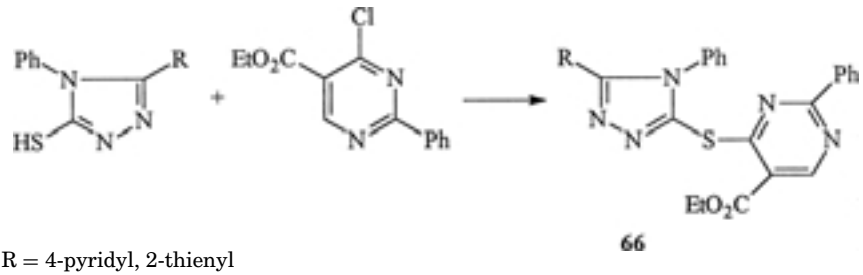


SCHEME 35

b. From Triazole Derivatives

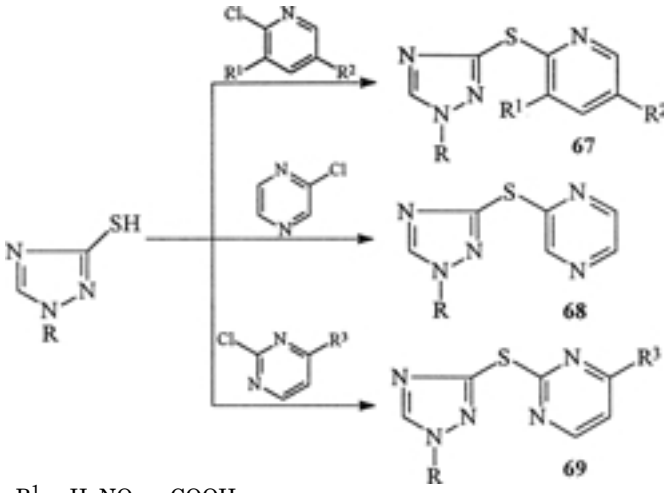
3-aryl-4-phenyl-1,2,4-triazole-5-thiols[39] reacted with ethyl-4-chloro-2-phenylpyrimidine-5-carboxylate to give the corresponding thioethers **66**.

Various derivatives **67–69** of triazole[40] substituted in the 3-position were synthesized by the reaction of 3-mercaptotriazoles with heterocyclic halides.



R = 4-pyridyl, 2-thienyl

SCHEME 36



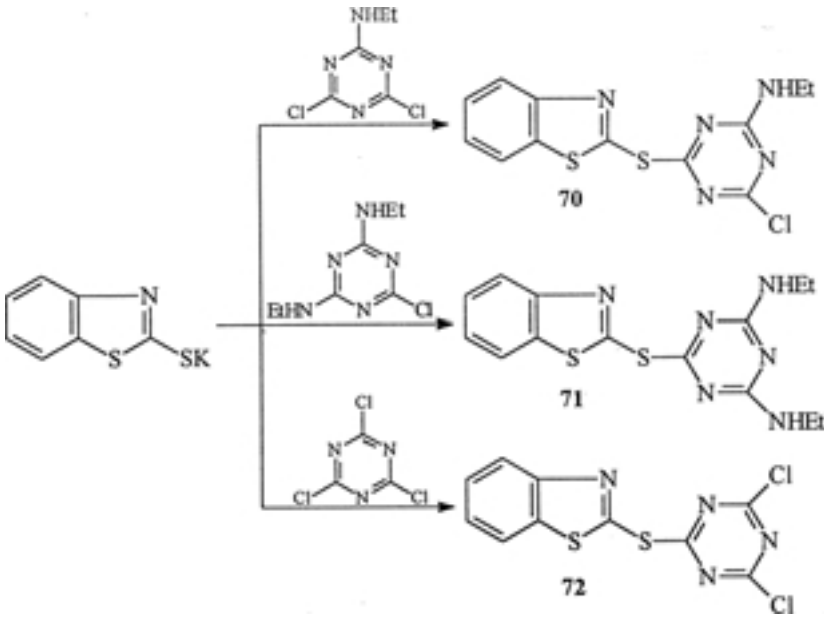
R = H, Me, R^1 = H, NO_2, —COOH
R^2 = H, 5-NO_2, 6-OH, 6-OMe
R^2 = H, MeO

SCHEME 37

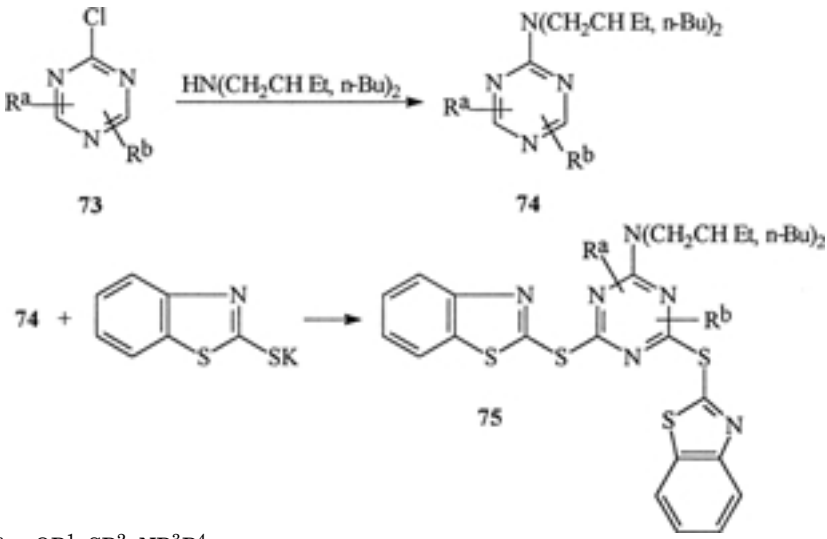
c. From Benzothiazole Derivatives

The potassium salt of 2-mercaptobenzothiazole reacted with amino-dichloro-1,3,5-triazine, diaminochloro-1,3,5-triazine or trichloro-1,3,5-triazine to give benzothiazolyl thiotriazines[41] **70–72**.

(Benzothiazolylthio)triazine[42] **75** was prepared as lubricant additives. Thus, cyanuric chloride **73** was aminated by $HN(CH_2CH$ Et, n-Bu$)_2$, followed by thioetherification of the product **74** by 2-mercapto benzothiazole, to afford **75**. Also, 2,4-diarylamino-6-(benzothiazol-2-ylthio)-s-triazines[43] **76** were prepared by reacting 2,4-diarylamino-6-chloro-s-triazines with 2-mercaptobenzothiazole.

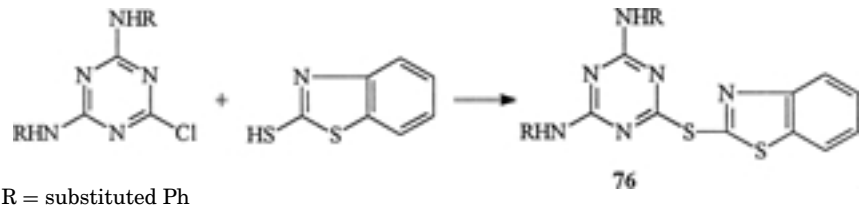


SCHEME 38



$R^a = OR^1, SR^2, NR^3R^4$
R^b = 2-benzothiazolylthio
$R^1, R^3, R^4 = H$, $R^2 = C_{1\text{-}30}$ alkyl, Ph, Naphthyl

SCHEME 39

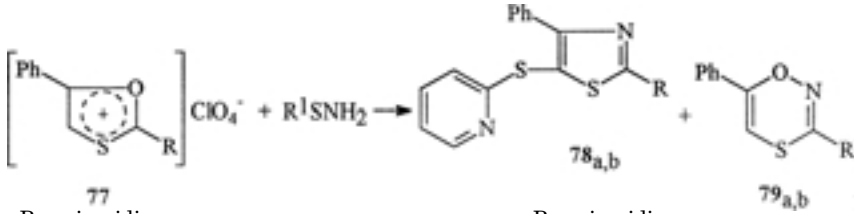


R = substituted Ph

SCHEME 40

d. Miscellaneous Syntheses

The reaction of 1,3-oxathiolium salts $\mathbf{77}_{a,b}$ with sulfenamide[44] gave 4-phenyl-2-piperidino(morpholino)-5-(pyridyl-2′ -ylthio)thiazoles $\mathbf{78}_{a,b}$ together with 6-phenyl-3-piperidino(morpholino)-1,4,2-oxathiazines $\mathbf{79}_{a,b}$, respectively.



77

a: R = piperidino
b: R = morpholino
R: 2-pyridyl

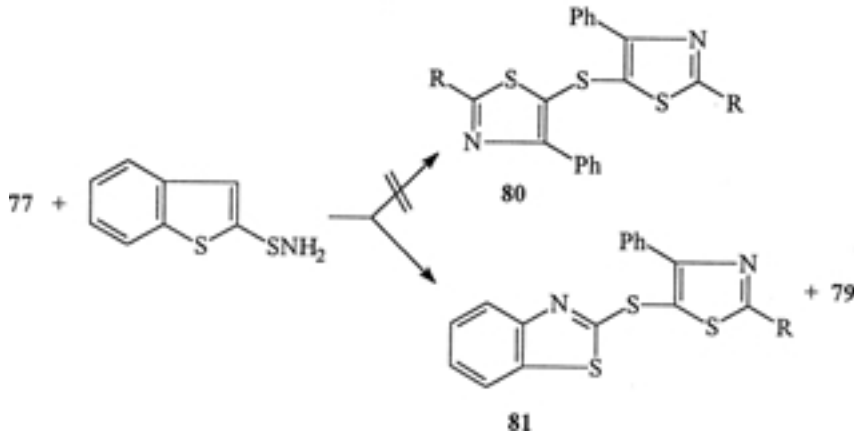
a: R = piperidino
b: R = morpholino

SCHEME 41

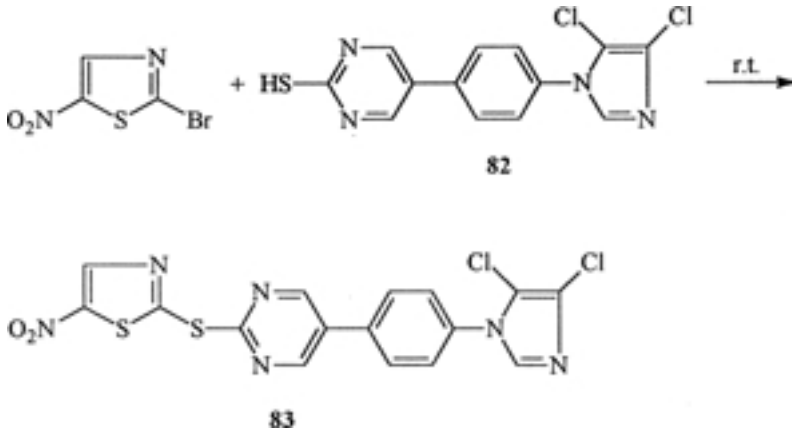
On the other hand, the reaction of **77** with 2-benzothiazole sulfenamide[44] did not give bis(2-morpholino-4-phenyl-5-thiazolyl)sulfide **80**, but gave **79** in low yield and a new type of product, namely a (2-benzothiazolyl-2-morpholino-4-phenyl-5-thiazolyl) sulfide **81.** Although the mechanism of the reaction remains in doubt, it is apparent at least that the overall pathway for the formation of **81** is composed of an addition of 2-benzothiazole sulphenamide to **77**, including cleavage of the sulfenamide S—N bond and elimination of H_2O and $HClO_4$ with respect to mass balance.

In addition, 2-bromo-5-nitrothiazole reacted with 4-[4-(4,5-dichloroimidazole-1-yl)phenyl-2-mercaptopyrimidine (**82**) at r.t. to give 4-(imidazolylphenyl)-2-(thiazolylthio)pyrimidine **83**.[45]

The reaction of chloromethyl methyl sulfoxide with sodium salt of 5-aryl-2-mercapto-1,3,4-thiadiazole[46] in refluxing ethanol furnished **84**. The nucleophilic addition of the sulfur-stabilized carbanion (generated by the action of sodium methoxide on **85** in methanol at r.t.) to C=N of thiosemicarbazones **85**, followed by quenching with dil. HCl, afforded



SCHEME 42



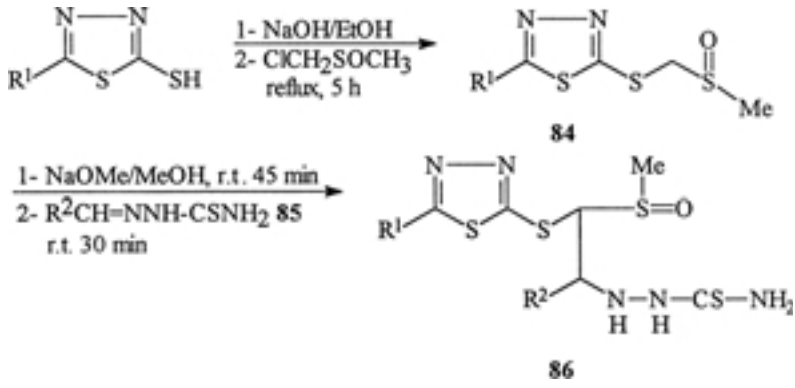
SCHEME 43

86, which, on treatment with 90% sulfuric acid at 0–5°C underwent a new intramolecular cyclization involving the acid labile methane sulfinyl leaving group to furnish **89**. It is interesting to note that the *Pummerer* rearrangement products **87** were not obtained at all in the synthesis.

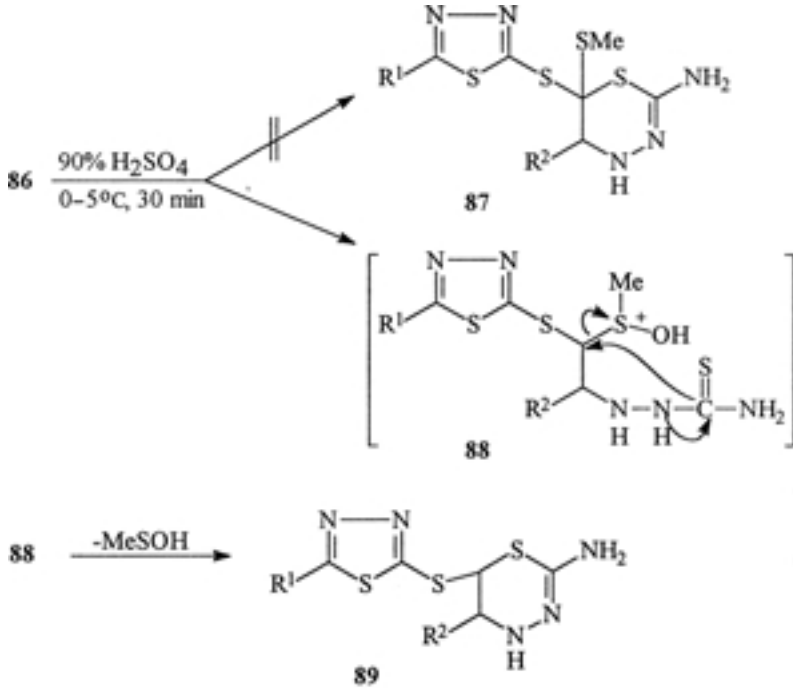
3. Synthesis of Diheterocyclic Sulfides Containing (5-5) Heterocyclic Rings

a. From Triazole Derivatives

The reaction between 3-aryloxymethyl-4-phenyl-5-mercapto-*s*-triazoles $\mathbf{90}_{a-c}$ with equimolecular amounts of 3-chloro-2,4-



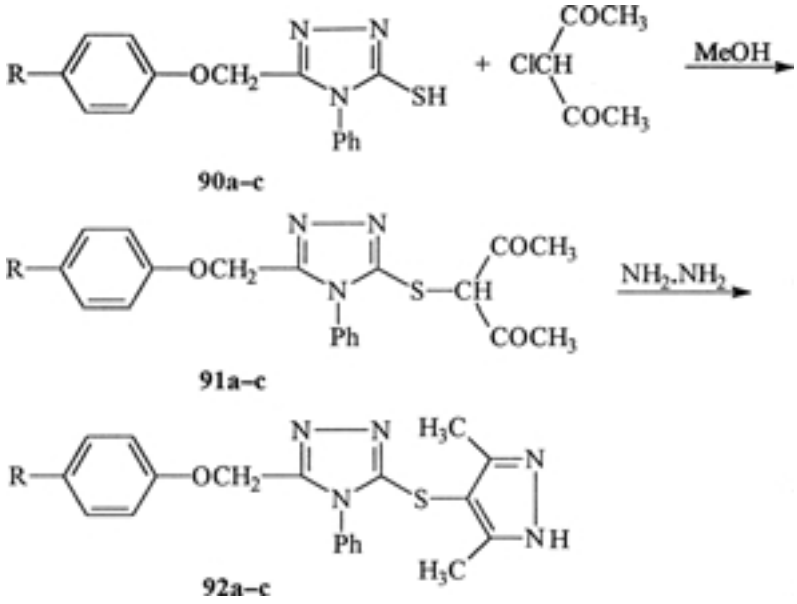
SCHEME 44



84: R^1 = Ph, 2-ClC_6H_4, 4-ClC_6H_4-
85: R^2 = Ph, 4-ClC_6H_4, 3-$NO_2C_6H_4$-
86–89: R^1 = Ph, 2-ClC_6H_4, 4-ClC_6H_4-;
R^2 = Ph, (2)-, (3)-, (4)-ClC_6H_4, 3-NO_2-ClC_6H_4-

SCHEME 45

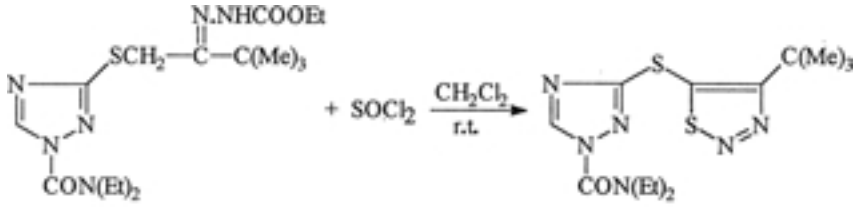
pentanedione in refluxing methanol gave the corresponding 5-(2′,4′-diketopentan-3-yl)thio-*s*-triazole derivatives **91**$_{a-c}$, which underwent further reaction with hydrazine hydrate to furnish 3-aryloxymethyl-4-phenyl-5-(3′,5′-dimethylpyrazol-4′-yl)thio-*s*-triazoles[47] **92**$_{a-c}$ in excellent yields.



a, R = H; b, R = CH_3; c, R = Cl

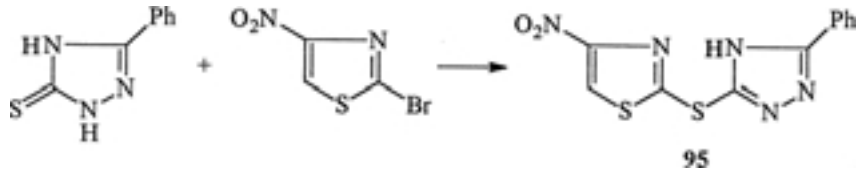
SCHEME 46

3-(1,2,3-thiadiazolylthio)-1,2,4-triazole-l-carboxamide derivative **94** was synthesized as an agrochemical. Thus, thionyl chloride was added to a solution of 1-(*N*,*N*-diethylcarbamoyl)-3-(3-ethoxycarbonyl hydrazone-2,2-dimethyl-butan-4-ylthio)-1*H*-1,2,4-triazole[48] **93** in CH_2Cl_2 at r.t. to give 1-(*N*,*N*-diethylcarbamoyl)-3-(4-tert-butyl-1,2,3-thiadiazol-5-ylthio)-1*H*-1,2,4-triazole(**94**).



SCHEME 47

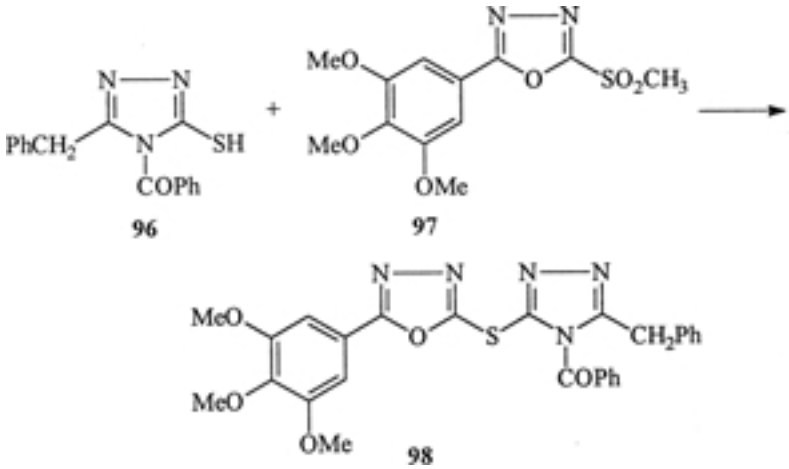
The reaction between 3-phenyl-1,2,4-triazole-5-thione with 2-bromo-5-nitro-thiazole afforded the sulfide **95**.[49]



95

SCHEME 48

The synthesis of (3-benzyl-4-benzoyl-1,2,4-triazol-5-yl)[5-(3,4,5-trimethoxy phenyl)-1,3,4-oxadiazol-2-yl]sulfide[50] (**98**) was achieved from the nucleophilic displacement of 3-benzyl-4-benzoyl-1,2,4-triazole-5-hydrosulfuryl anion **96** on the 2-position of 2-methylsulfonyl-5-(3,4,5-trimethoxyphenyl)-1,3,4-oxadiazole **97**.



96 **97** **98**

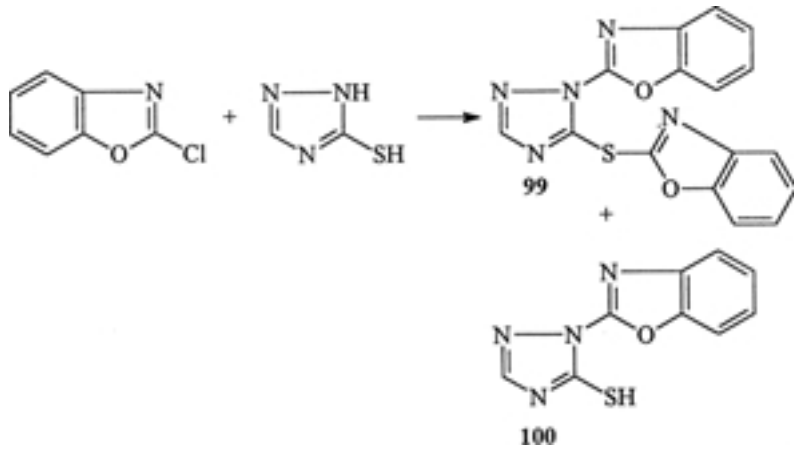
SCHEME 49

The reaction between 2-chlorobenzoxazole and 1,2,4-triazole-2-thiol[51] gave 2-[(2-benzoxazolyl)-1,2,4-triazolo-2-yl)]thiobenzoxazole (**99**) and 2-benzoxazolyl-3-mercapto-1,2,4-triazole (**100**).

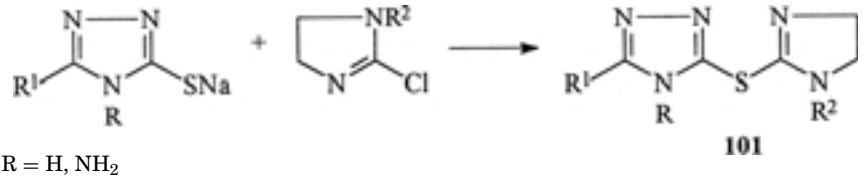
The reaction of sodium salts of the substituted 1,2,4-triazole-3-thiones[52] with 2-chloro-4,5-dihydroimidazole in an aqueous or alcoholic solution afforded the corresponding triazolyl imidazolinyl sulfides **101**.

b. From Thiazole and Benzothiazole Derivatives

2-[4-(4-bromophenylthiazol-2-yl)thio]benzothiazole (**102**) was formed by the reactions of $RCOCH_2SCN$ and 2-benzothiazoline



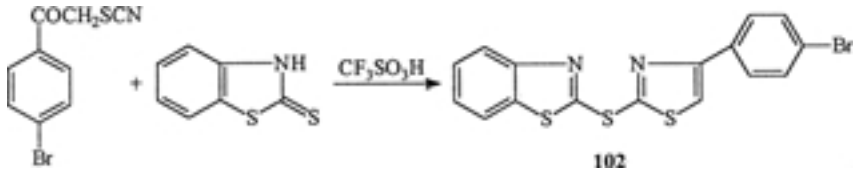
SCHEME 50



$R = H, NH_2$
R^1 = Ph, 4-pyridyl, pyrazolinyl, $3,5(MeO)_2C_6H_3$; $R^2 = H$

SCHEME 51

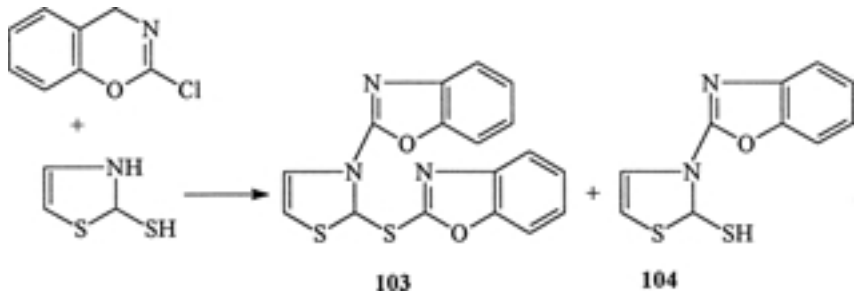
thione.[53] Thus, 4- $BrC_6H_4COCH_2SCN$ in 1,2-dichloroethane reacted with benzothiazoline thione in the presence of a catalytic amount of CF_3SO_3H to give **102** in an excellent yield.



SCHEME 52

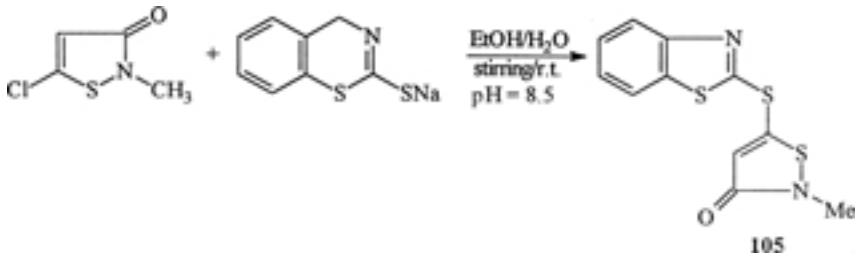
The reaction of 2-chlorobenzoxazole with 2-thiazolin-2-thiol gave 2-(heterocyclylthio)benzoxazole[51] **103** and 2-heteroarylbenzoxazole **104**.

To prepare (4-isothiazolin-3-one-5-ylthio)benzothiazole[54] **105**, a mixture of 5-chloro-2-methyl-4-isothiazolin-3-one and sodium salt of 2-mercaptobenzothiazole was stirred in ethanol/water (pH 8.5) at r.t. for one day.



103 **104**

SCHEME 53



105

SCHEME 54

c. Miscellaneous Syntheses

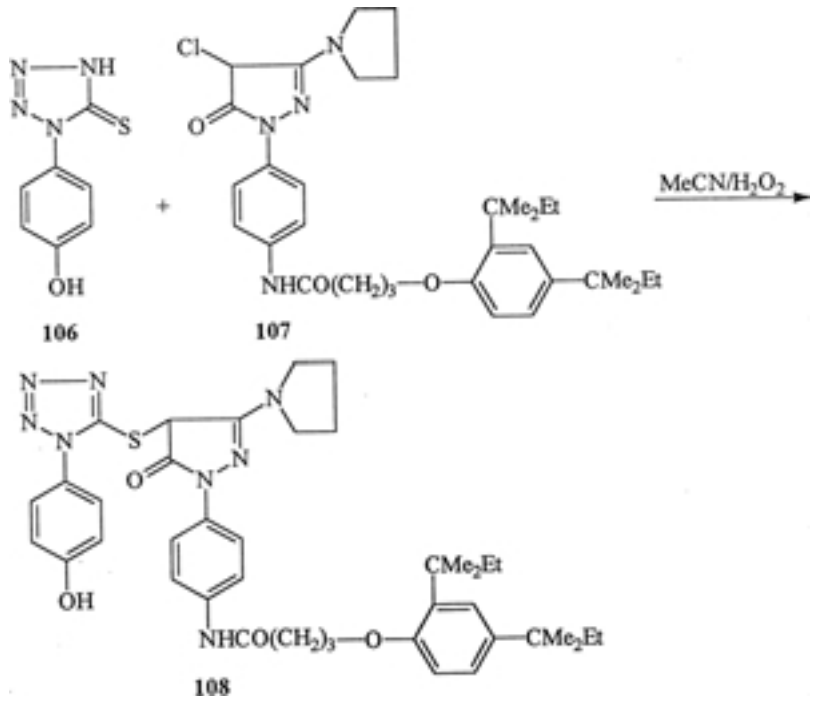
Heterocyclic thioethers were synthesized by the treatment of CH acids $R^1R^2CH_2$ (R^1 = H, alkyl, aryl, aryl carbonyl, oxycarbonyl, R^2 = carboxy, alkoxy, aryloxycarbonyl or arylcarbonyl, cyano, nitro) or $R^1R^2CH_2$ = cycloalkanone, tetralone; indanone) with C-mercapto-substituted imidazoles, thiazoles, or 1,2,4-thiadiazoles, in an organic solvent in the presence of H_2O_2.[55] Thus, I-(*p* hydroxyphenyl)-5-mercaptotetrazole (**106**) reacted with the pyrazolinone derivative **107** using H_2O_2 in acetonitrile to afford **108**.

Spontaneous transformation of furanthiols to thiolactones[56] **109** was observed and Et_3N accelerated this process.

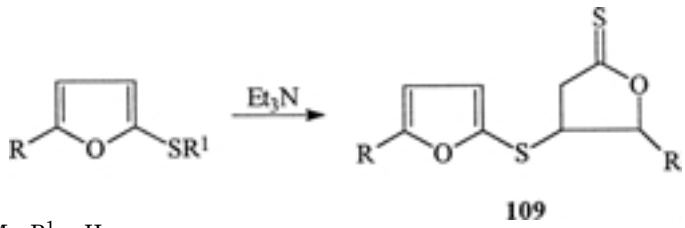
The thermal reaction of 2-thiophenethiol[57] with acetylene (1:1) at 500–600°C gave sulfide **110** (76%).

The adduct **111** (obtained by the nucleophilic addition of sulfenylated DMSO derivative to thiosemicarbazone) underwent a new intramolecular cyclization[58] involving deoxygenative demethylation to yield 2-(4-phenyl-2-thiocarbamoyl-1,2,3-thiadiazol-5-yl)-5-phenyl-1,3,4-oxadiazole (**112**) on treatment with $SOCl_2$.

Bis(3-chloro-1,2,4-thiadiazol-5-yl) sulfide **113** was synthesized by the reaction of 3-chloro-5-methanesulfonyl-1,2,4-thiadiazole with aqueous Na_2S inEtOH at r.t.[59]



SCHEME 55



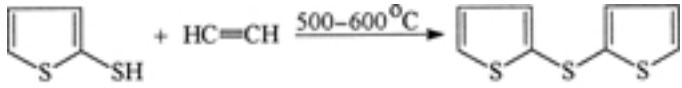
R = H, Me; R^1 = H

SCHEME 56

4. The Synthesis of Arylheterocyclic Sulfides Contaning a 6-Membered Heterocyclic Ring

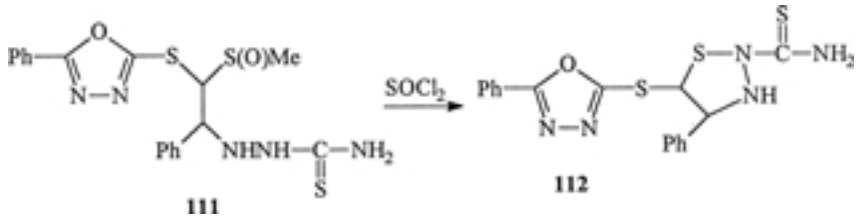
a. From Pyrimidine Derivatives

The synthesis of 2-amino-5[(4-chlorophenyl)thio]-4(3*H*)-pyrimidinone[60] (**114**) A from 2-amino-5-bromo-4-(3*H*)pyrimidinone began with the displacement of the bromo group in the pyrimidine by 4-chlorophenylthiolate in *N,N*-dimethyl formamide in presence of K_2CO_3.



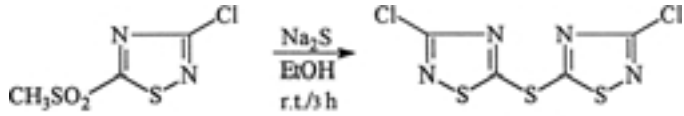
110

SCHEME 57



111 **112**

SCHEME 58



113

SCHEME 59

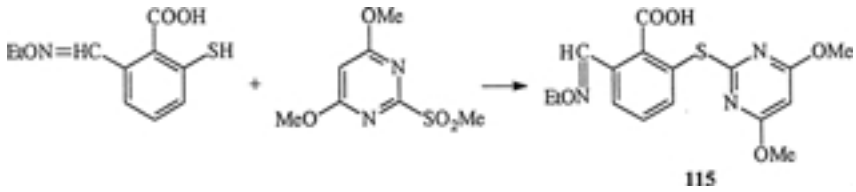
114

SCHEME 60

Ethyl 2-acetylthio-6-bromomethyl benzoate was oxidized to 2,6-AcS(HCO)$C_6H_3CO_2$Et and then treated with aminoethoxide to give 2,6-AcS(EtON=CH)$C_6H_3CO_2$Et, which, after hydrolysis with 50% aq. NaOH, gave 2,6-EtON=CH(SH)C_6H_3COOH. The latter reacted with 4,6-dimethoxy-2-methanesulfonyl pyrimidine to give the benzaldoxime thioether derivative **115**.[61]

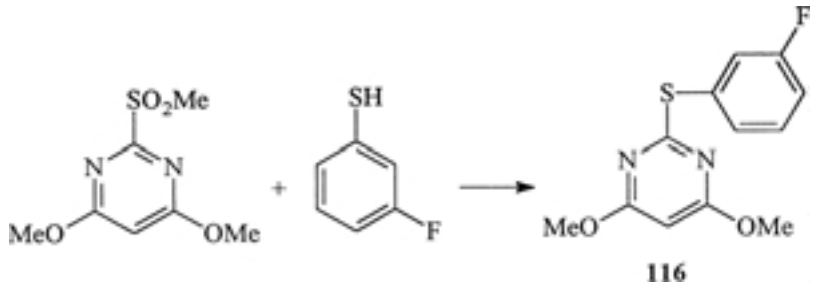
The reaction between 4,6-dimethoxy-2-methylsulfonylpyrimidine with 3-fluorothiophenol gave phenylthiopyrimidine derivative **116**.[62]

6-phenyl-2-(4,6-dimethoxypyrimidinylthio)benzoic acid (**118**) was prepared as a herbicide.[63] 4,6-dimethoxy-2-methylsulfonylpyrimidine



115

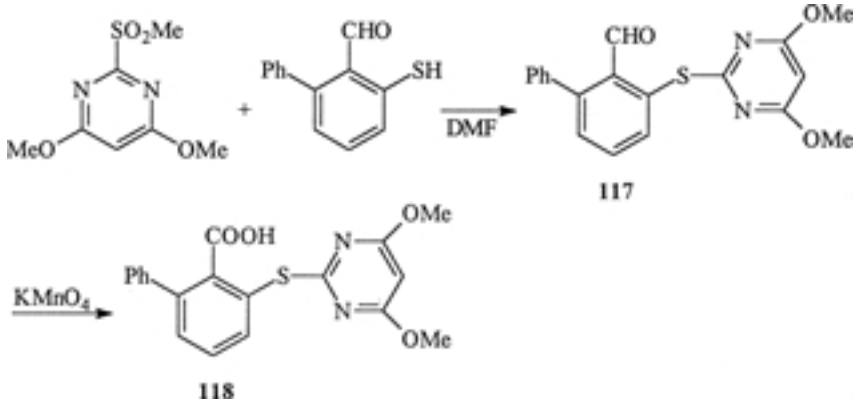
SCHEME 61



116

SCHEME 62

was added to 6-phenylthiosalicyaldehyde in DMF in the presence of K_2CO_3 to give the corresponding aldehyde **117**, which was oxidized by $KMnO_4$ to give the target compound **118**.



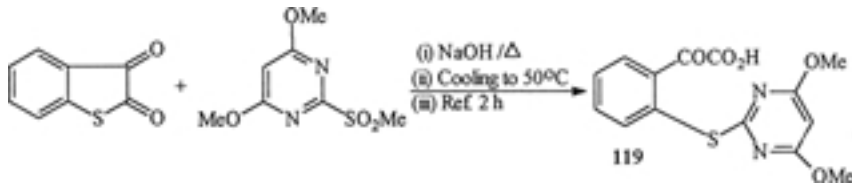
117

118

SCHEME 63

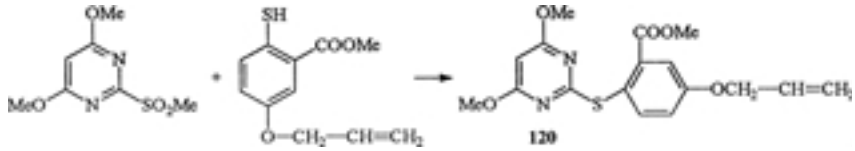
Benzothiophen-2,3-dione reacted in aqueous NaOH and with 4,6-dimethoxy-2-methylsulfonylpyrimidine to give the sulfide **119**.[64]

A mixture 4,6-dimethoxy-2-methylsulfonylpyrimidine and methyl-5-alloxy-2-thiobenzoate in 2-butanone in presence of K_2CO_3 was refluxed



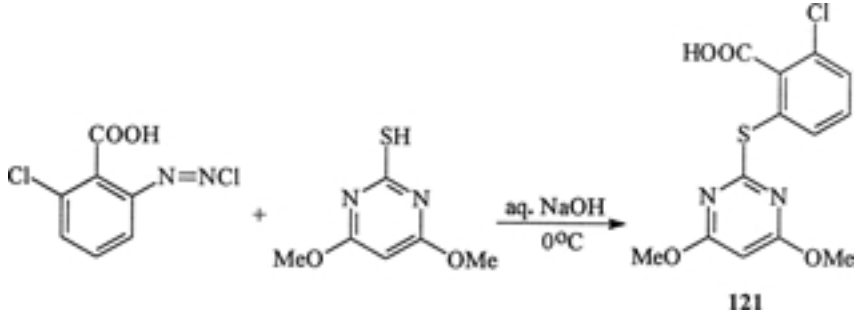
SCHEME 64

to give methyl 5-allyloxy-2-(4,6-dimethoxypyrimidin-2-yl)thiobenzoate (**120**).[65]



SCHEME 65

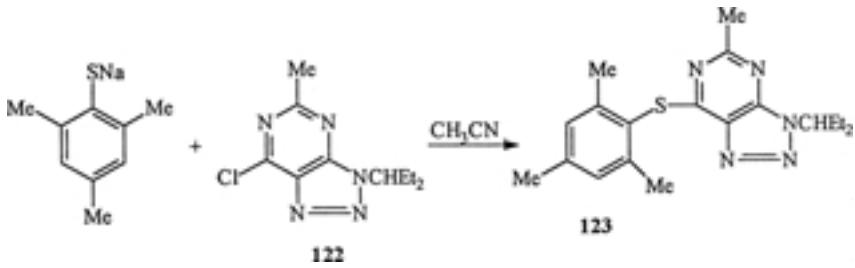
2-[(carboxy-substituted-phenyl)thio]-4,6-dimethoxypyrimidine was prepared by thiation of diazotized aniline 3,2-R(HO_2C)$C_6H_3NH_2$ with 4,6-dimethoxy-2-mercaptopyrimidine.[66] Thus, a solution of 2-amino-6-chloro-benzoic acid HCl was added to a mixture of a pyrimidine derivative in aqueous NaOH at r.t. to give **121**.



SCHEME 66

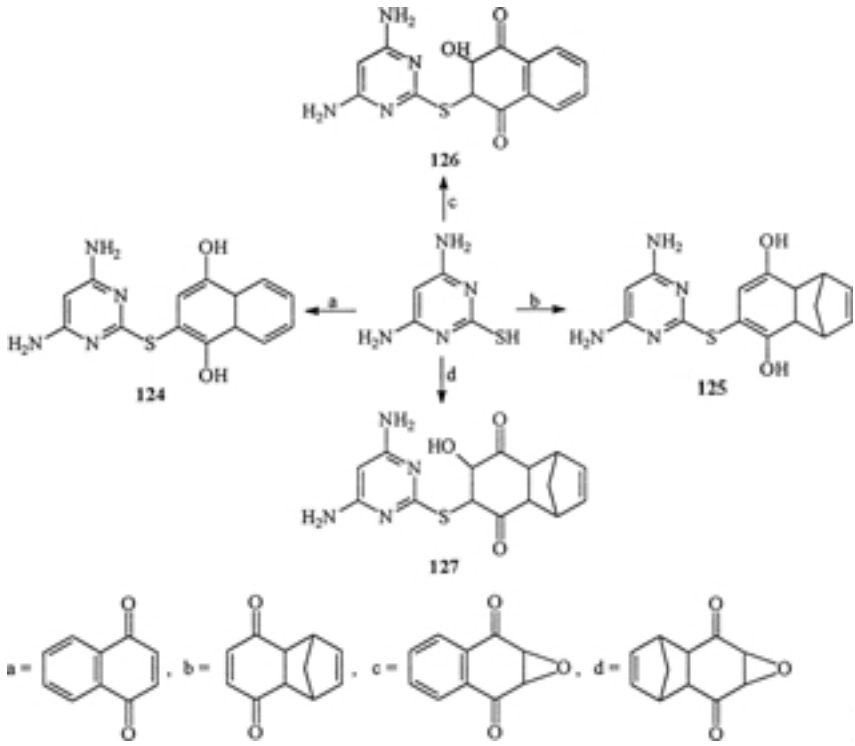
The synthesis of arylthio-fused triazolopyrimidines **123** as CRF receptor antagonists[67] was carried out by the treatment of 2,4,6-trimethylthiophenol with NaOMe in methanol followed by the reaction of the resulting salt with 7-chloro-3-(1-ethylpropyl)-5-methyl-3*H*-1,2,3-triazolo [4,5-*d*]pyrimidine(**122**) in acetonitrile.

The reaction of 4,6-diamino-2-mercaptopyrimidine with napthoquinone or benzoquinone-cyclopentadiene adduct[68a] gave **124** and **125**,



SCHEME 67

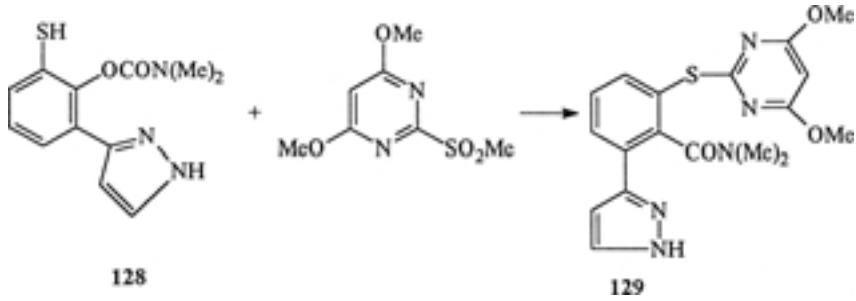
respectively. The reaction of this pyrimidine with epoxides afforded **126** and **127**, respectively.



SCHEME 68

The metalation of 3-pyrazolyl-2-(*N*,*N*-dimethyloxycarbonyl)-thiophenol (**128**) with NaH in DMF, followed by the treatment with 2-methylsulfonyl-4,6-dimethoxypyrimidine gave 6-pyrazolyl-2-(4,

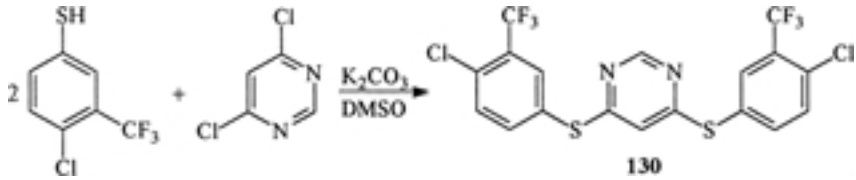
6-dimethoxypyrimidin-2-ylthio)-1-(*N,N*-dimethylaminocarbonyl)benzene (**129**).[69]



128 129

SCHEME 69

The reaction between 4-chloro-3-trifluoromethylthiophenol with 4,6-dichloro-pyrimidine in DMSO in the presence of K_2CO_3[70] gave 4,6-bis(4-chloro-3-trifluoromethylphenylthio)pyrimidine (**130**) (94%).



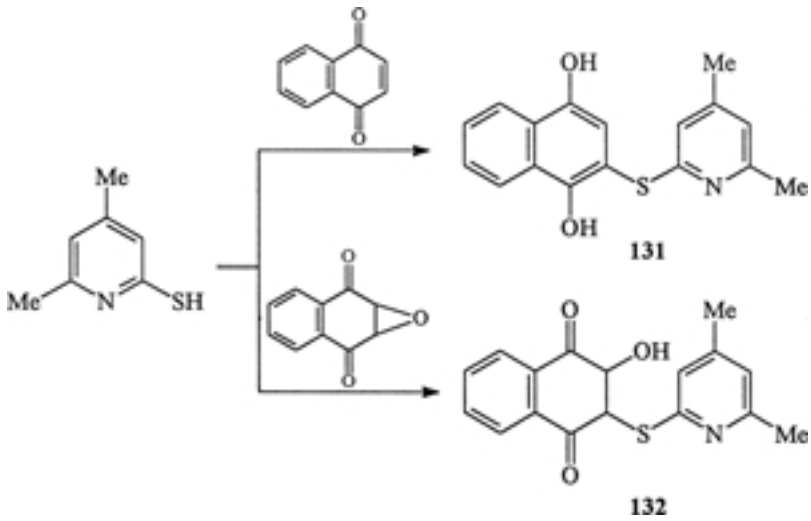
130

SCHEME 70

b. From Pyridine Derivatives

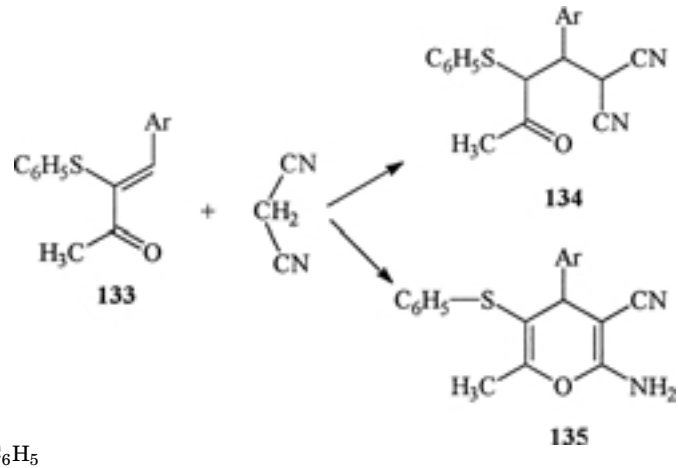
The reaction of 1,4-naphthoquinone and its epoxide with 2-mercapto-4,6-dimethylpyridine hydrochloride confirmed that the meraptocontaining heterocycle adds to the quinone at the conjugated system and to the epoxides with cleavage of the epoxides ring to give the corresponding thiohydroquinones and hydroxythiohydroquinones.[68b] Thus, treating 1,4-naphthoquinone with 2-mercapto-4,6-dimethylpyridine gave the hydroquinone derivative **131**. A similar reaction with oxirenonaphthoquinone gave the corresponding hydroxynap-thoquinone **132**.

The Michael addition of malononitrile, cyanoacetamide, and ethylcyanoacetate with α, β unsaturated ketones containing a phenylthio group at the α-position and phenyl, 4-methoxyphenyl, 4-nitrophenyl, 4-pyridyl, and *N,N*-dimethylamino at the β-carbon determined the influence of the phenylthio group as well as that of the aryl, pyridyl, and dimethylamino substituents.[71] Thus, heating $\mathbf{133}_a$ with malononitrile in the presence of $C_5H_{11}N/CH_3CN$ resulted the noncyclic Michael



SCHEME 71

adduct **134**$_a$, but, in the presence of $C_5H_{11}N$/boiling EtOH, the pyran derivative **135**$_a$ was obtained. Similarly, the reaction of **133**$_{b,c}$ with malononitrile yielded the corresponding derivative of **135**$_a$.

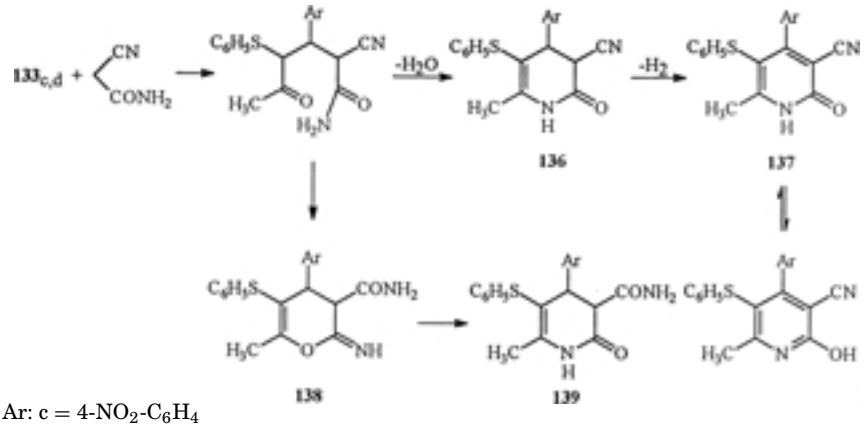


Ar: a = C_6H_5
b = 4-CH_3O-C_6H_4
c = 4-NO_2-C_6H_4
d = 4-pyridyl

SCHEME 72

The reaction of compound $\mathbf{133}_{c,d}$ with cyanoacetamide[71] in boiling EtOH/$C_5H_{11}N$ afforded the products 2-hydroxy-6-methyl-5-(phenylthio)-4-(4-nitrophenyl)-3,4-dihydropyridine-3-carbonitrile ($\mathbf{136}_c$), 2-hydroxy-6-methyl-5-(phenylthio)-4-(4-nitrophenyl)pyridine-3-carbonitrile ($\mathbf{137}_c$), and 2-hydroxy-6-methyl-5-(phenyl-thio)-4-(4-nitrophenyl)-3,4-dihydropyridine-3-carboxamide ($\mathbf{139}_c$).

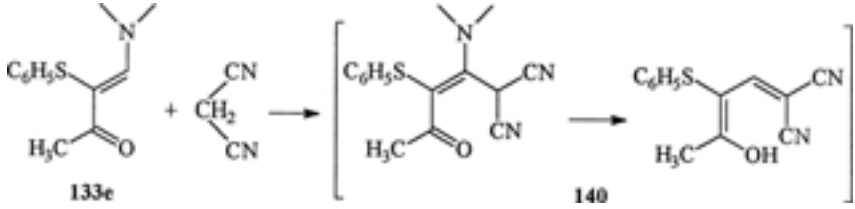
Compound $\mathbf{137}_c$ was obtained by the dehydrogenation of $\mathbf{136}_c$. The reaction of $\mathbf{133}_{c,d}$ with cyanoacetamide involved in the first step the formation of a Michael adduct, which then underwent cyclization to 2-pyridone $\mathbf{136}_c$ by the elimination of H_2O. The reaction of $\mathbf{133}_d$ with cyanoacetamide gave the pyridone $\mathbf{137}_d$.



Ar: c = 4-NO_2-C_6H_4
d = 4-pyridyl

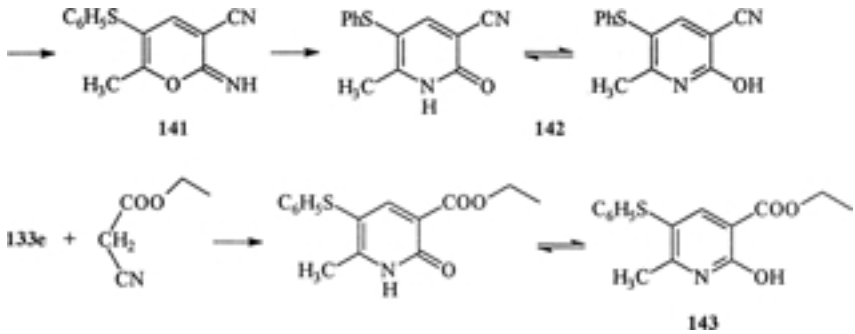
SCHEME 73

The reaction of compound $\mathbf{133}_e$ containing a dimethylamino group in the β-position with malononitrile in ethanolic solution in the presence of piperidine led to the formation of the pyridine derivative[71] **142**. Then the addition of malononitrile to $\mathbf{133}_e$ gave rise to the Michael adduct **140**, which subsequently eliminated dimethylamine and underwent cyclization to the iminopyran **141** as an intermediate. The presence of piperidine and $(CH_3)_2NH$ in the reaction mixture promotes the ring transformation of **141** to the 2-pyridone **142**. Moreover, the reaction of $\mathbf{133}_e$ with cyanoacetamide gave 2-hydroxy-6-methyl-5-(phenyl-thio)pyridine-3-carbonitrile **142**, while its reaction with ethylcyanoacetate gave 3-ethoxycarbonyl-2-hydroxy-6-methyl-5-(phenylthio)pyridine (**143**).



133e 140

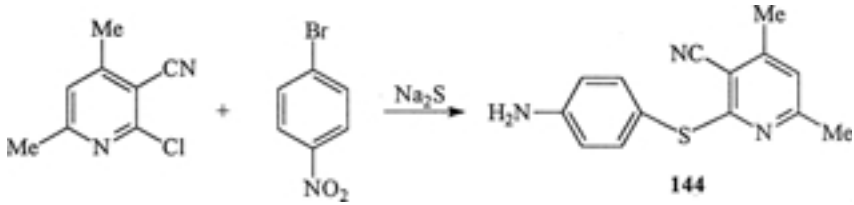
SCHEME 74



141 142 143

SCHEME 75

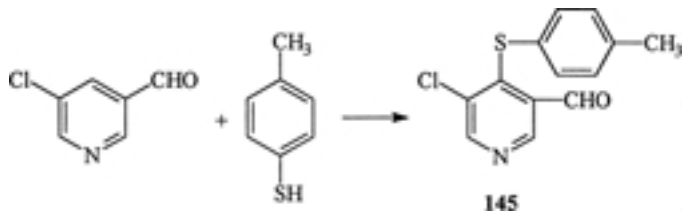
Aminophenylthiopyridine derivative **144** was prepared by the reaction of 2-chloro-3-cyano-4,6-dimethylpyridine and 4-bromonitrobenzene in an aqueous sodium sulfide solution.[72]



144

SCHEME 76

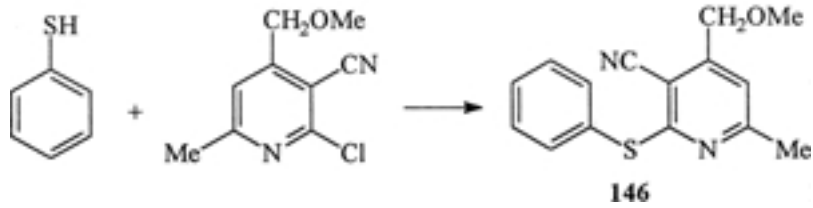
3,5-dichloropyridine was carbonylated, and the product was thioetherified by 4-methylthiophenol to give 4-(methylphenylthio)-5-chloro-4-pyridine carbox-aldehyde (**145**).[73]



145

SCHEME 77

Cathodic reduction of an aromatic thiol[74] in the presence of 2-chloro-4-(methoxymethyl)-6-methyl-3-pyridinecarbonitrile gave 4-(methoxymethyl)-6-methyl-2-(phenylthio)pyridine-3-carbonitrile (**146**).

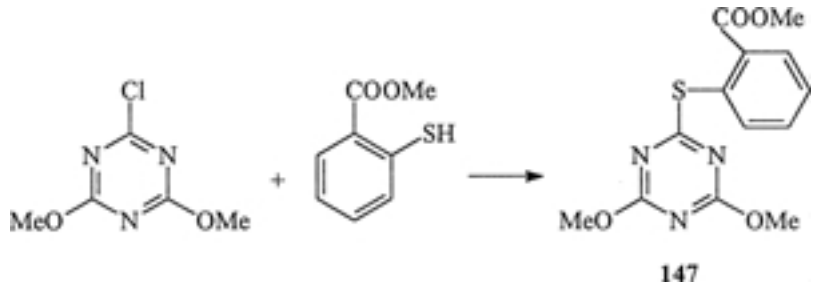


146

SCHEME 78

c. From Triazine Derivatives

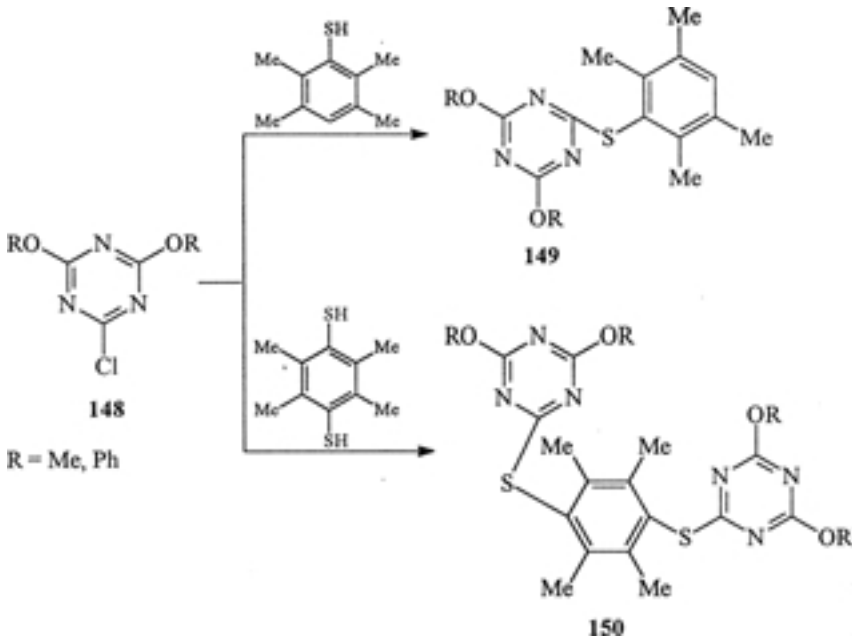
Triazine derivative[75] **147** was obtained by refluxing 2-chloro-4,6-dimethoxytriazine with methyl 2-mercaptobenzoate in 2-butanone containing K_2CO_3.



147

SCHEME 79

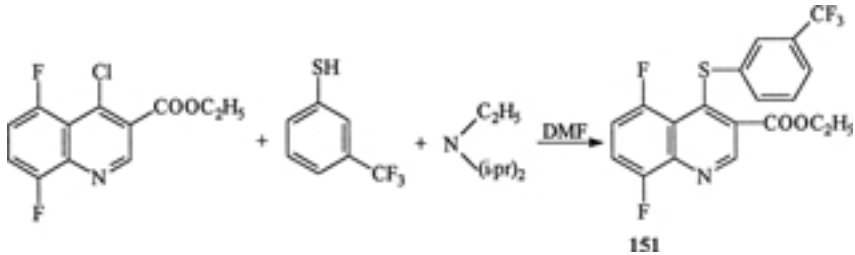
The reaction of 2-chloro-4,6-dimethoxytriazine or 4,6-diphenoxy-1,3,5-triazine **148** with monomercapto and dimercapto compounds[76] in aqueous NaOH gave mono- and bis-4,6-dimethoxy or 4,6-diphenoxy-1,3,5-triazine-2-thiohydrocarbon **149** and **150**, respectively.



SCHEME 80

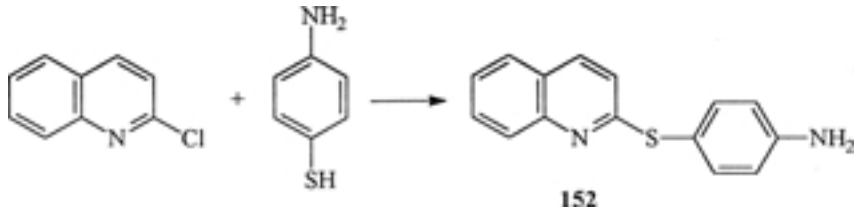
d. From Quinoline Derivatives

A mixture of 4-chloro-3-ethoxycarbonyl-5,8-difluoroquinoline, 3-trifluoro-methylthiophenol, and diisopropylethylamine was stirred in DMF giving 3-ethoxycarbonyl-5,8-difluoro-4-(3-trifluoromethylphenylthio)quinoline **151**.[77]



SCHEME 81

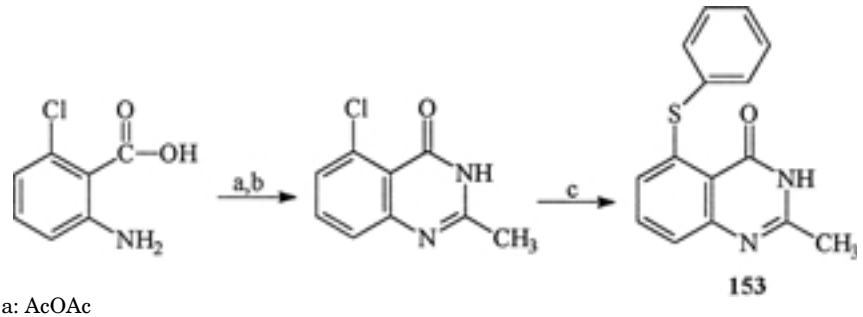
In addition, 2-chloroquinoline was thioetherified by 4-mercaptoaniline to afford 2-(4-aminophenylthio)quinoline **152**.[78]



SCHEME 82

e. From Quinazolinone Derivatives

The synthesis of 2-methyl-5-(phenylsulfanyl)-3*H*-quinazolin-4-one[31] (**153**) was achieved from the reaction of 5-chloro-2-methyl-3*H*-quinazolin-4-one (prepared from an anthranilic acid derivative) and thiophenol in DMA in the presence of NaH, Cu_2O, and CuBr.



a: AcOAc
b: NH_3; aqueous 1N NaOH
c: NaH, DMA, CuBr, $Cu_2O + C_6H_5SH$

SCHEME 83

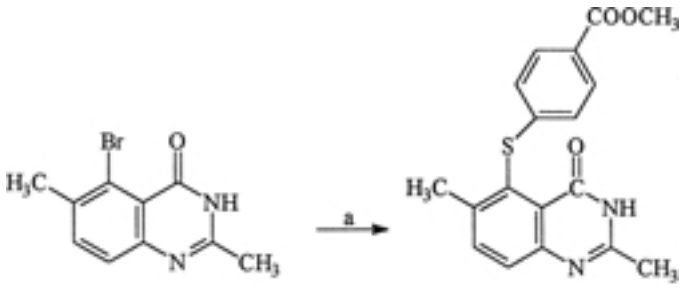
Also, the reaction between 5-bromo-2,6-dimethyl-3*H*-quinazolin-4-one with methyl 4-mercaptobenzoate[31] afforded methyl 4-[(2,6-dimethyl-4-oxo-3,4-dihydroquinazoline-5-yl)thio]benzoate (**154**).

f. Miscellaneous Syntheses

6-substituted-2,4-bis(trichloromethyl)-s-triazine **155** containing a sterically hindered phenol fragment was synthesized by the reaction of a phenol derivative with trichloroacetonitrile in the presence of HC1 or HC1+A1Br_3.[79a]

Also, 6-substituted-2,4-bis(arylthio)-s-triazines **156** were prepared by the reaction of carboxyimidate esters R-C(=NH)OEt with arylthiocyanate[79b] R^1SCN.

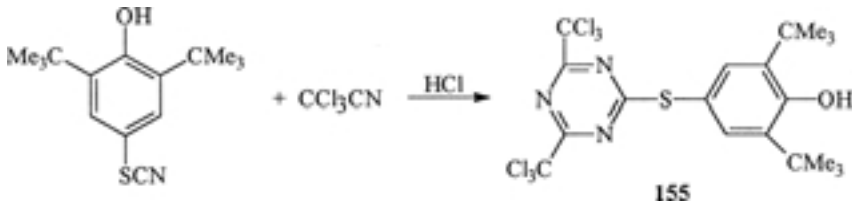
Cyclocondensation of 2-furonitrile with aminoguanidine nitrate gave 3-amino-5-(2-furyl)-1,2,4-triazole (**157**), which was further



154

a: NaH, DMA, CuBr, Cu_2O + 4(HS)$C_6H_4CO_2CH_3$

SCHEME 84



155

SCHEME 85

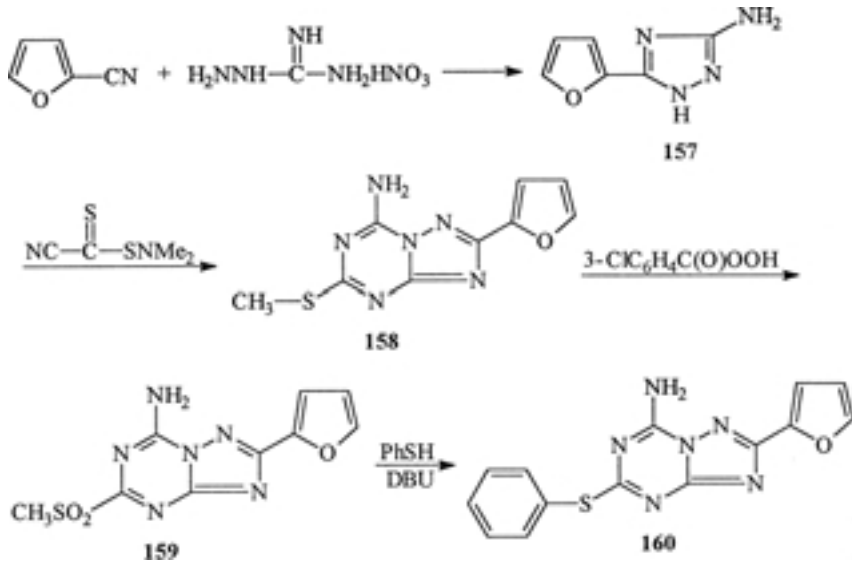
156

R = 4,3,5-(OH)$(Me_3C)_2C_6H_2SCH_2$, 5-nitro-2-furyl,
2-(5-nitro-2-furyl)vinyl, indol-3-yl, indol-3-ylmethyl,
2- or 3-pyridyl
R^1 = 4,3,5(OH)$(Me_3C)_2C_6H_2$

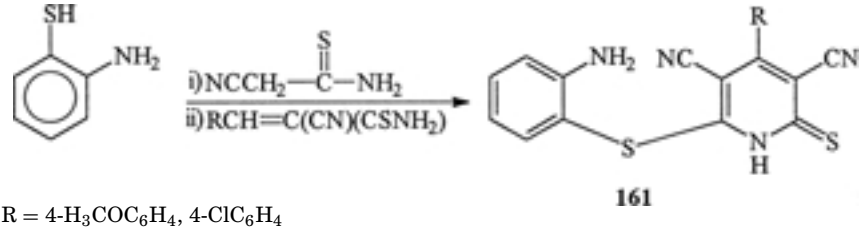
SCHEME 86

cyclized with dimethyl *N*-cyanodithioiminocarbonate to give amino(furyl)triazolotriazine derivative (**158**). The S-oxidation of the latter with 3-chloroperbenzoic acid gave the sulfone derivative **159**, which underwent a substitution reaction with thiophenol and DBU in refluxing dimethoxy ethane to give a phenylthio derivative of amino(furyl)-triazolotriazine **160**.[80]

A novel synthesis of pyridine derivatives utilized *o*-aminobenzenethiol and α,β-unsaturated nitriles as starting compounds. Thus, the condensation of *o*-aminobenzenethiol with cyanothioacetamide and



SCHEME 87



R = 4-$H_3COC_6H_4$, 4-ClC_6H_4
2-furanyl, 2-thienyl

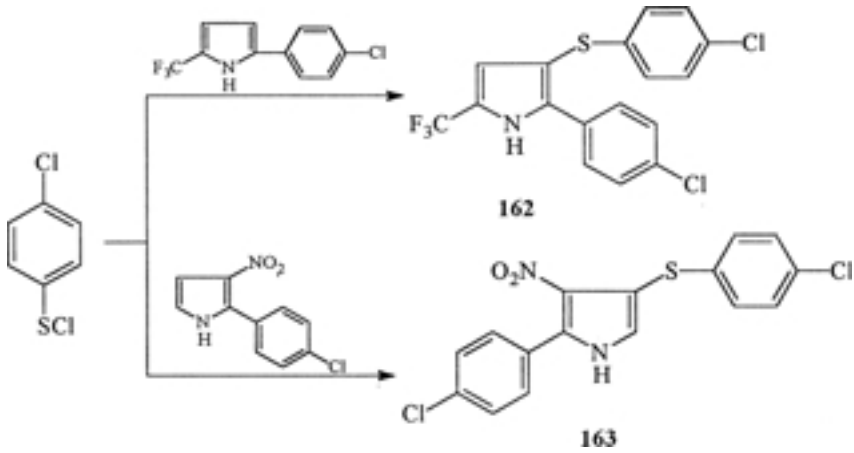
SCHEME 88

RCH=C(CN)($CSNH_2$) gave the substituted phenylthiopyridine derivatives **161**.[81]

5. The Synthesis of Arylheterocyclic Sulfides Containing 5-Membered Heterocyclic Ring

a. From Pyrrole Derivatives

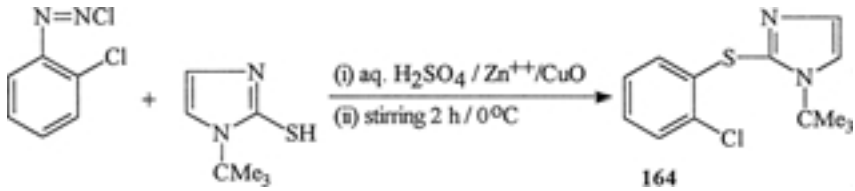
The reaction of *p*-chlorophenylsulfenyl chloride with 2-(*p*-chlorophenyl)-5-trifluoromethyl pyrrole[82a] in methylenechloride afforded the corresponding sulfide **162** while 2-(*p*-chlorophenyl)-3-nitropyrrole **163** was produced.



SCHEME 89

b. From Imidazole Derivatives

2-(phenylthio)imidazole[83] derivative **164** was synthesized as an anti-inflammatory agent by adding diazotized *o*-chloroaniline to a mixture comprising aq. H_2SO_4 containing Zn^{++}, CuO, and l-*tert* butyl-2-mercaptoimidazole.

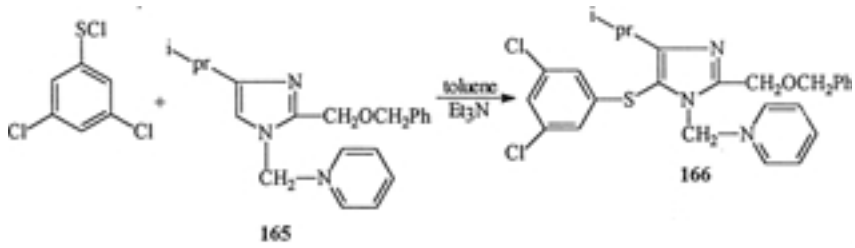


SCHEME 90

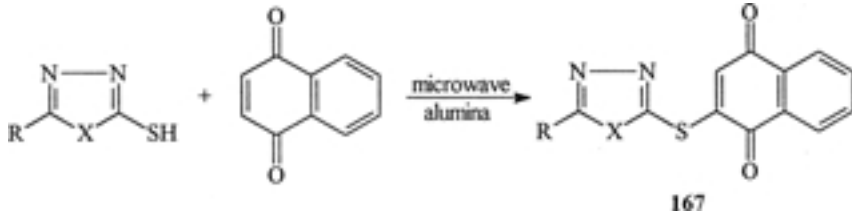
Also, the reaction of 3,5-dichlorobenzenesulfenyl chloride[84] in toluene with the imidazole derivative **165** in the presence of triethylamine gave the corresponding sulfide **166** (81%).

b. From Thiadiazole and Oxadiazole Derivatives

A rapid thiolation of 1,4-napthoquinone at the C-2 position occurred by using 2-mercapto-5-alkyl-1,3,4-oxadiazole/thiadiazole in dry media using neutral alumina as a solid support under microwave irradiation.[85] Thus, 2-mercapto-5-alkyl-1,3,4-thiadiazole or oxadiazole reacted with 1,4-naphthoquinone to give 2-thio[5′-alkyl-1′,2′,4′-thiadiazole/oxadiazole]-1,4-naphthoquinone **167**.

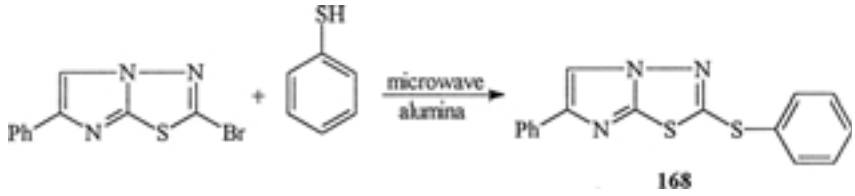


SCHEME 91



SCHEME 92

2-(phenylthio)-6-phenylimidazo[2,1-*b*]-1,3,4-thiadiazole (**168**) was prepared by the reaction of 2-bromo-6-phenylimidazo[2,1-*b*]-1,3,4-thiadiazole with benzenethiol.[86]

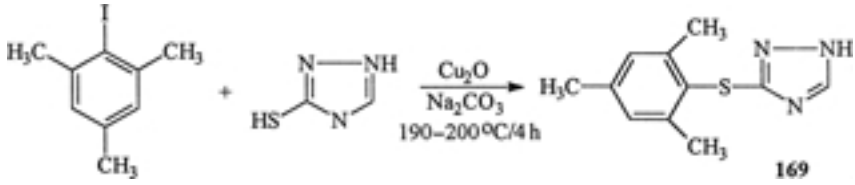


SCHEME 93

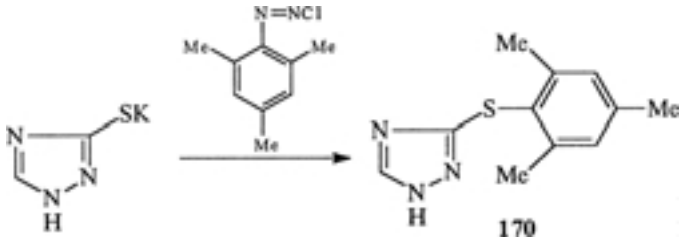
d. From Triazole Derivatives

3-(2,4,6-trimethylphenylthio)-1*H*-1,2,4-triazole (**169**) was prepared by the reaction of 1,3,5-trimethyl-2-iodobenzene (iodomesitylene) with an alkali metal salt of 3-mercapto-1*H*-1,2,4-triazole[87] in the presence of a Cu catalyst or in DMI containing Na_2CO_3 and Cu_2O at 190–200°C.

Phenylthiotriazole derivatives as intermediate for herbicides were prepared via the the reaction of a benzene diazonium salt with mercaptotriazole. Thus, the potassium salt of mercaptotriazole (prepared from 3-mercapto-1*H*-1,2,4-triazole with KOH in methanol or from thiosemicarbazide with formaldehyde mixed with KOH in methanol) reacted



SCHEME 94

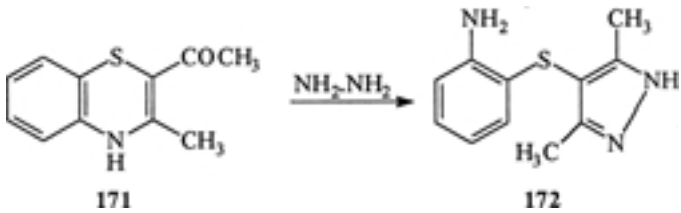


SCHEME 95

with the diazonium salt of 2,4,6-trimethylaniline[88] in methanol to give 3-(2,4,6-trimethylphenylthio)-1*H*-1,2,4-triazole (**170**).

e. From the Ring Opening of Benzothiazine

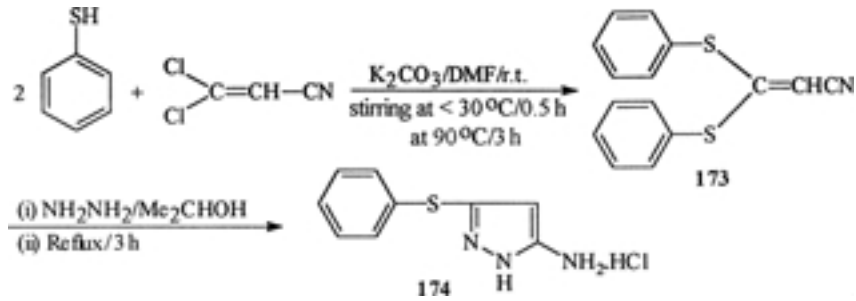
Owing to the presence of a carbonyl group, the benzothiazine **171** easily reacted with hydrazine affording[89] 4-(2′-aminophenylthio)-3,5-dimethyl pyrazole (**172**) as shown by the decolorization of the orange red solution, which is due to intramolecular cyclization of the formed hydrazone.



SCHEME 96

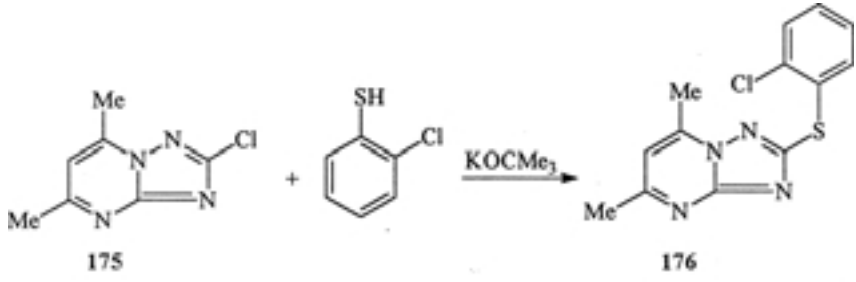
f. From Thiophenol Derivatives

The treatment of thiophenol with a mixture of K_2CO_3 and DMF at r.t. and with 1,1-dichloro-2-cyanoethylene[90] added to the previous mixture gave $(PhS)_2C{:}CHCN$ (**173**), a solution of which in isopropanol was treated with hydrazine to give **174** (65%).



SCHEME 97

2-chlorothiophenol in sulfolane containing $KOCMe_3$ reacted with 1,2,4-triazolo[1,5-*a*]pyrimidine **175** to give 2-(2-chlorophenylthio)-1,2,4-triazolo[1,5-*a*]-pyrimidine **176**.[91]

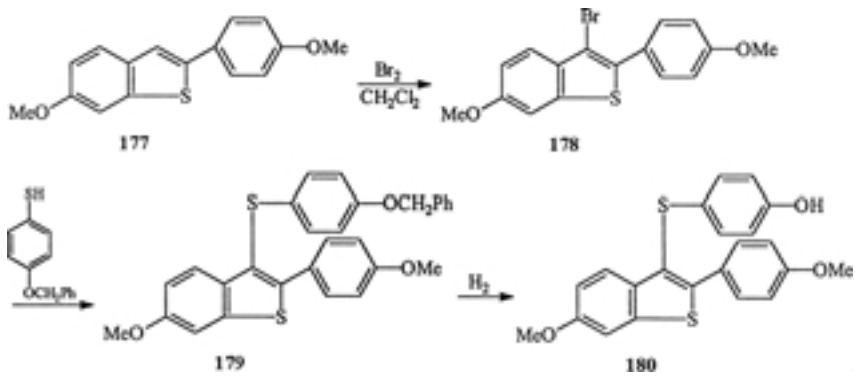


SCHEME 98

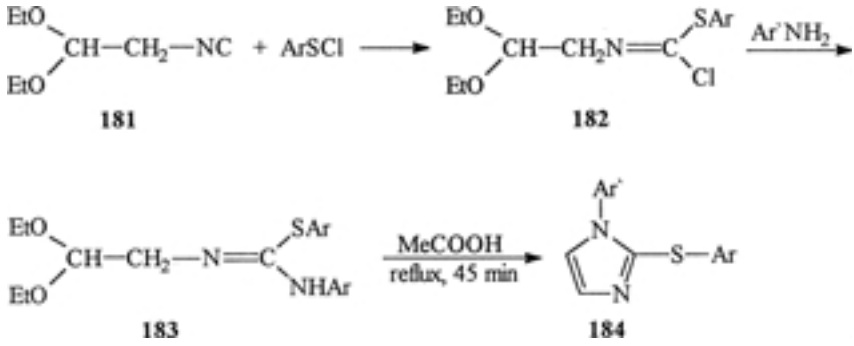
6-methoxy-2-(4-methoxyphenyl)benzo[*b*]thiophene underwent a sequence involving bromination at the 3-position with Br_2 in CH_2Cl_2 (100%), etherification[92] of the bromide 178 with 4-($PhCH_2O$)C_6H_4SH, and then hydrogenolysis of the benzyl ether **179**, to give 6-methoxy-2-(4-methoxyphenyl)-3-(4-hydroxyphenyl-thio)benzo[*b*]thiophene (**180**).

g. Miscellaneous Syntheses

A novel synthetic method to obtain 1-aryl-2-arylthio-1*H*-imidazoles[93] was based upon the use of 2,2-diethoxy-1-isocyanidoethane (**181**) (prepared by dehydrating the corresponding *N*-substituted formamide). The reaction between **181** and arylsulfenyl chlorides afforded *N*-(2,2-diethoxyethyl)-s-arylisothio-carbamoyl chlorides **182**, which reacted in situ with amines to give the corresponding isothioureas derivatives **183**. On heating crude **183** with acetic acid, a ring-closure reaction took place to give **184**.



SCHEME 99



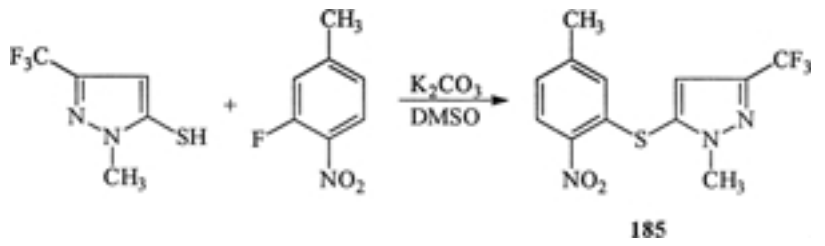
Ar: 4-ClC_6H_4	Ar: C_6H_5
4-ClC_6H_4	4-$CH_3C_6H_4$
4-ClC_6H_4	4-$CH_3OC_6H_4$
4-ClC_6H_4	3-ClC_6H_4
4-ClC_6H_4	4-ClC_6H_4
4-ClC_6H_4	3,5-diClC_6H_4
4-$CH_3C_6H_4$	4-$CH_3C_6H_4$
4-$CH_3C_6H_4$	4-ClC_6H_4

SCHEME 100

The reaction of 5-mercapto-1-methyl-3-trifluoromethylpyrazole with 3-fluoro-4-nitrotoluene[94] in DMSO in the presence of K_2CO_3 afforded 5-methyl-1-(1-methyl-3-trifluoromethyl-1*H*-pyrazole-5-yl)thio-2-nitrobenzene (**185**).

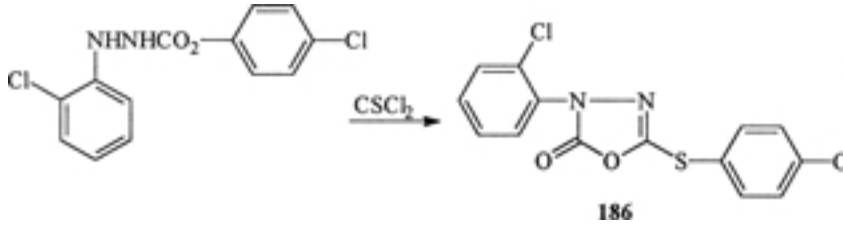
3-aryl-5-arylthio-1,3,4-thiadiazol-2(3*H*)-one derivative **186** was synthesized as an endoparasiticide via the cyclocondensation of 2-$ClC_6H_4NHNH(CO)_2C_6H_4Cl$-4 with $CSCl_2$.[95]

Substituted thioarylbenzo[*f*]quinolines **187** and **188** were obtained by the replacement of chlorine in 2-chloro-4-methylbenzo[*f*]quinoline



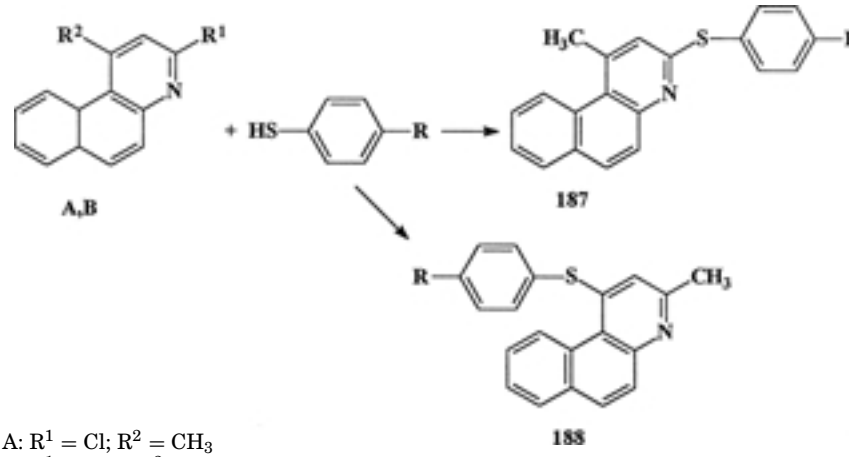
185

SCHEME 101



186

SCHEME 102



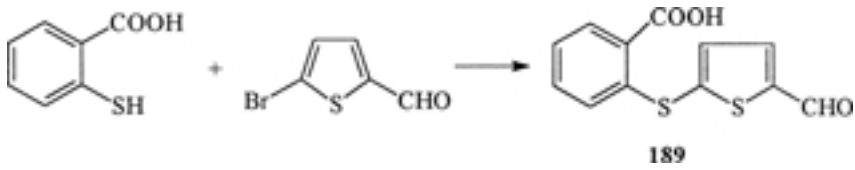
A: $R^1 = Cl$; $R^2 = CH_3$
B: $R^1 = CH_3$; $R^2 = Cl$

R: NH_2, NO_2

SCHEME 103

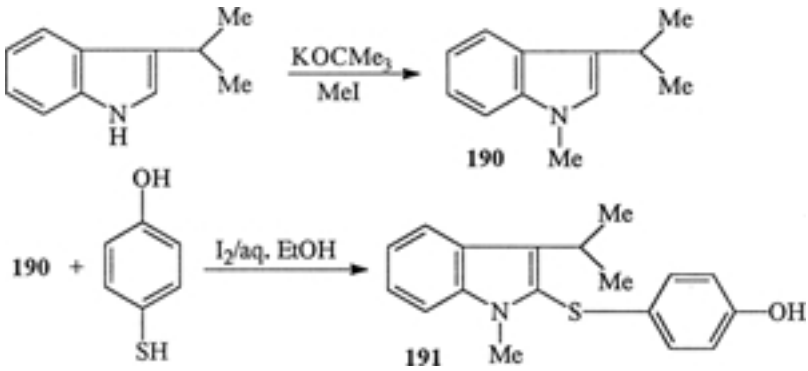
"**A**" and 4-chloro-2-methylbenzo[*f*]quinoline[96] "**B**" with thiols, respectively.

2-[(5-formyl-2-thienyl)thio)]benzoic acid **189** was prepared through the interaction of thiosalicylic acid and 5-bromothiophene-2-carboxaldehyde.[97a,b]



SCHEME 104

3-isopropylindole underwent *N*-methylation[98] using $KOCMe_3$ and methyl iodide to give **190**, which Was coupled with 4-HOC_6H_4SH using iodine in aqueous ethanol to give hydroxy-4-benzenethio derivative **191**.

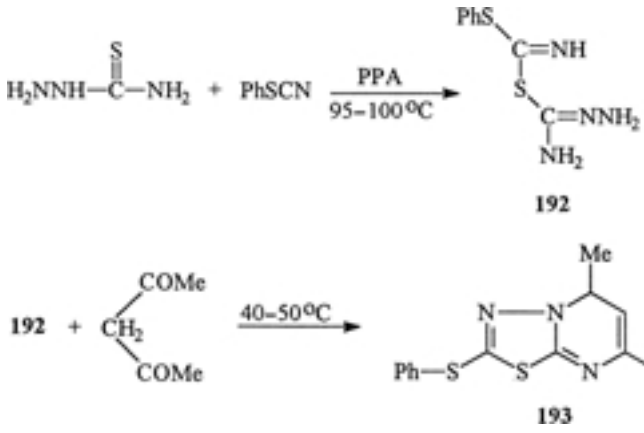


SCHEME 105

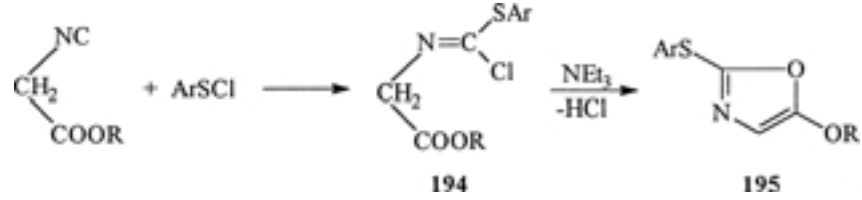
The treatment of thiosemicarbazide with phenylthiocyanate[99] in polyphosphoric acid, followed by condensing the intermediate with acetylacetone, gave 2-phenylthio-5,7-dimethyl-1,3,4-thiadiazole[3,2-*a*]pyrimidine (**193**).

2-arylthio-5-alkoxyoxazoles,[100] starting from alkyl isocyanoacetates, was obtained by the following synthetic method. The first step of this reaction consists of the addition of arylsulfenyl chlorides to the carbenoid carbon of alkyl isocyanoacetates to give *N*-alkoxycarbonylmethyl-*S*-arylisothiocarbamoyl chlorides **194**. The second step consists of the cyclization of **194** with NEt_3. The possible reaction pathway for the cyclization of isothio-carbamoyl chlorides was reported in Scheme 108.

The treatment of *N*-ethoxycarbonylmethyl-*S*-arylisothiocarbamoyl isothiocyanates[101] **196** (prepared in situ by the reaction of ethylisocyanoacetate with arylsulfenylthiocyanates in CH_2Cl_2, with NEt_3) resulted in an unexpected ring-closure reaction to afford 6-arylthio-8-ethoxycarbonyl-4-ethoxycarbonylmethyl-aminoimidazo[5,1-*b*][1,3,5]thiadiazine-2-thione (**197**).

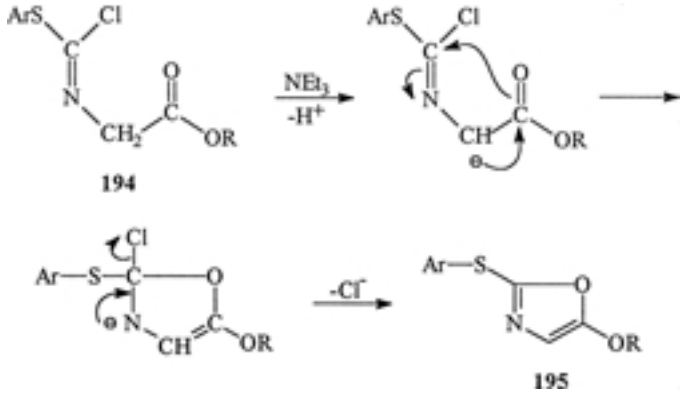


SCHEME 106



Ar = Phenyl, 4-chloro-2-nitrophenyl, 2-nitrophenyl, 4-chlorophenyl, 4-methylphenyl
R = Me, Et

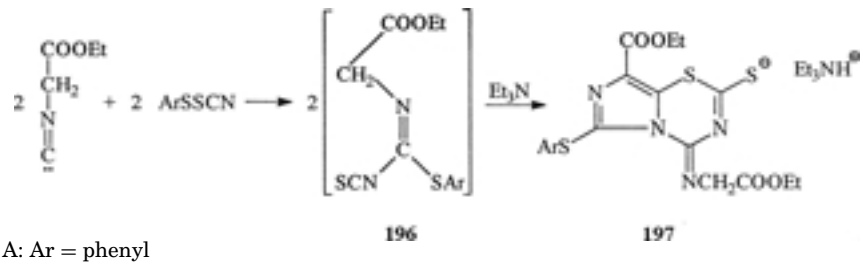
SCHEME 107



SCHEME 108

A possible reaction pathway[101] was reported in Scheme 110.

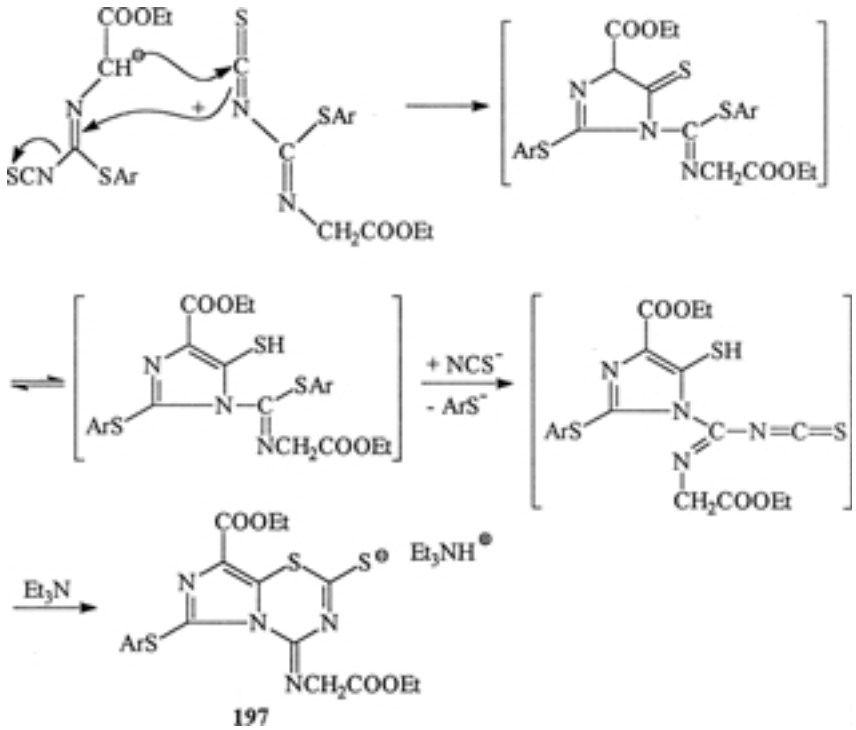
The starting materials used to obtain 4-(arylthio)-3-methylfuroxans **200** and 3-(arylthio)-4-methylfuroxans **201** were 1-(arylthio)-2-methylglyoximes **199**. The latter compounds were synthesized starting



196 197

A: Ar = phenyl
b: Ar = 4-chlorophenyl

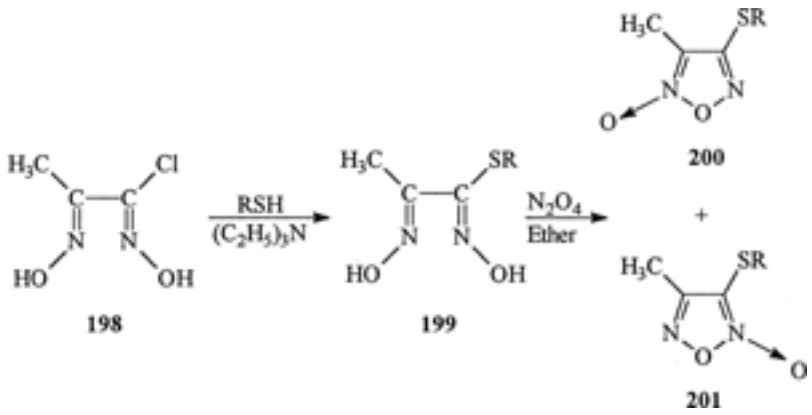
SCHEME 109



197

SCHEME 110

from anti-1-chloro-2-methylglyoxime **198** and the appropriate thiols,[102] in ether solution, in the presence of triethylamine. The oxidation of **199** with dinitrogen tetroxide gave a mixture of furoxans (**200** and **201**) that were obtained.



$R = C_6H_5$; 4-$CH_3C_6H_4$; 4-$CH_3OC_6H_4$; 4-ClC_6H_4; 4-FC_6H_4

SCHEME 111

CHEMICAL REACTIONS OF SULFIDES

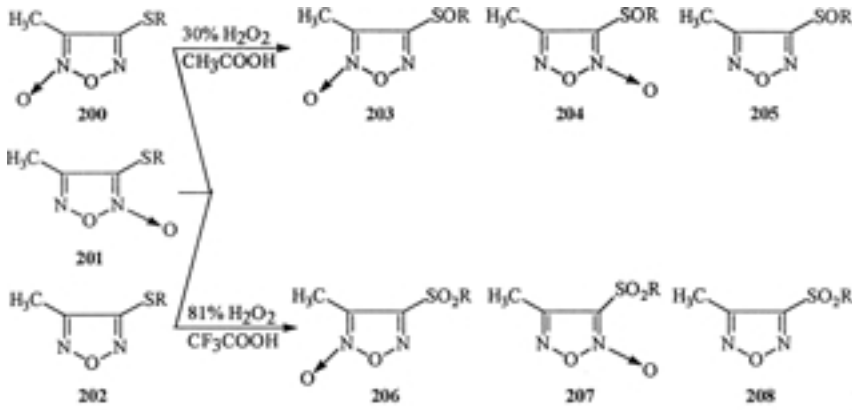
a. Oxidation

Sulfides are oxidized to sulfoxides or sulfones. The best general reagent for this oxidation is 30% hydrogen peroxide.[103–108] Sulfoxides are isolated in the oxidation of the corrsponding sulfides when a limited quantity of reagent is used in acetone or acetic acid solution at r.t. With more peroxide and sometimes a higher temperature, the corresponding sulfones are isolated. In acetic acid solution, the active oxidizing agent is peracetic acid.[109] This reagent is improved by using a carboxylic acid in the presence of a mineral acid or organic sulfonic acid catalyst. Other oxidizing agents include perbenzoic acid,[107] potassium permanganate,[103,110] and chromic anhydride.[103,105]

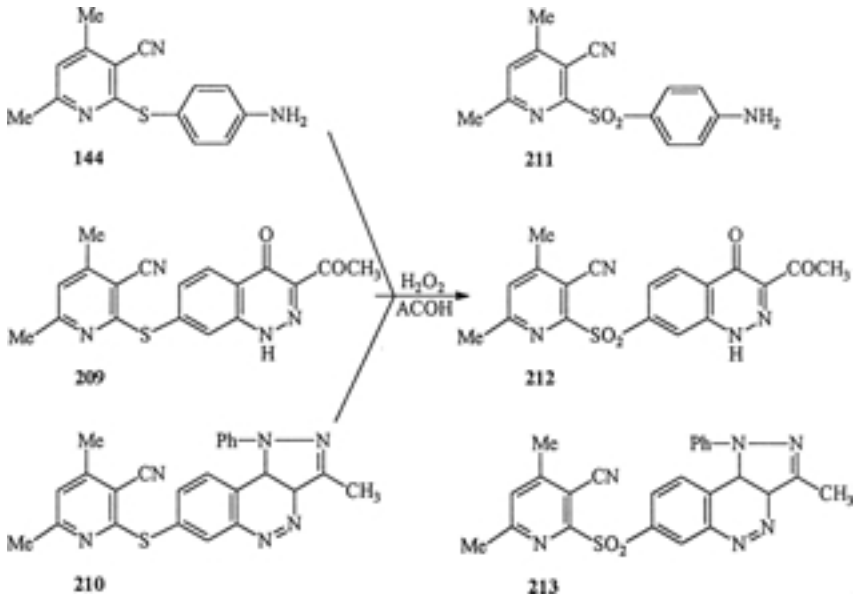
Arylthio derivatives **200–202** ($R = C_2H_5$) were oxidized with equimolcular amounts of 30% H_2O_2 in acetic acid solution to afford the corresponding phenyl sulfinyl analogs[102] **203–205** in fair yields. By contrast, an excess of 81% H_2O_2 in trifluoroacetic acid solution afforded the arylsulfonyl derivatives **206–208** in high yields.

Oxidation of some phenylthiopyridine derivatives[72] **144**, **209**, and **210** with hydrogen peroxide in acetic acid afforded the corresponding sulfones **211–213**, respectively.

Phenylthiopyrimidine derivative **214** was oxidized[111] by *m*-chloroper-benzoic acid and gave the corresponding sulfone derivative **215**. The s-oxidation of hydroxy-4-benzenethio derivative **191** with *m*-chloroper-benzoic acid[98] gave the corresponding sulfone **216**.



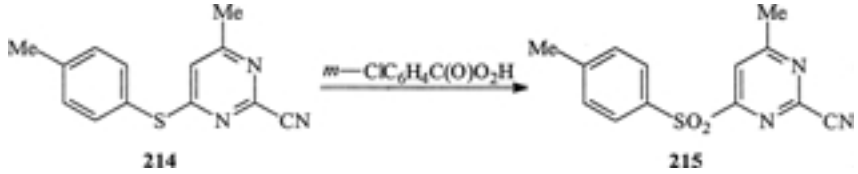
SCHEME 112



SCHEME 113

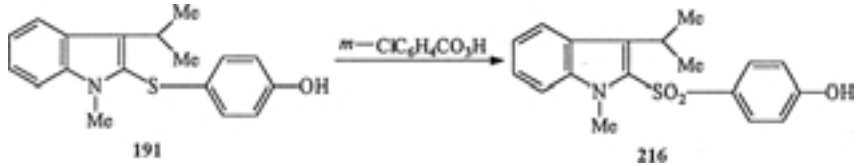
The oxidation of 1-(*N*,*N*-diethylcarbamoyl)-3-(4-*tert* butyl-1,2,3-thiadiazol-5-ylthio)-1*H*-1,2,4-triazole (**94**) by *m*-chloroperbenzoic acid in CH_2Cl_2[48] under reflux gave 1-(*N*,*N*-diethylcarbamoyl)-3-(4-*tert* butyl-1,2,3-thiadiazol-5-ylsulfonyl)-1*H*-1,2,4-triazole (**217**).

The permanganate oxidation of sulfide derivatives[96] **187** and **188** afforded the corresponding sulfones **218** and **219**, respectively.



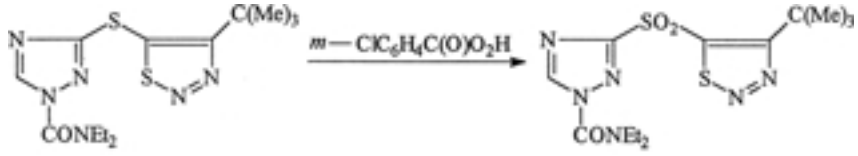
214 215

SCHEME 114



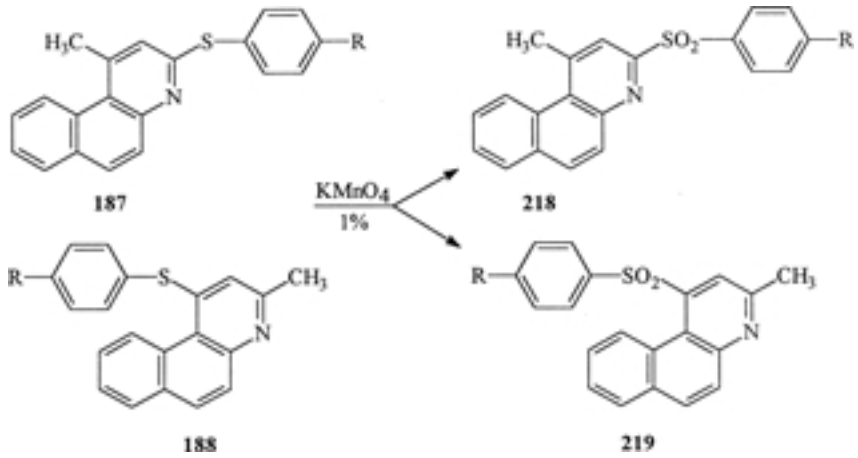
191 216

SCHEME 115



94 217

SCHEME 116



187 218 188 219

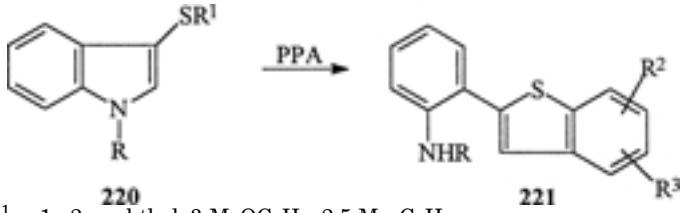
SCHEME 117

b. Rearrangement

(i) Structural Rearrangement

The unexpected acid-catalyzed rearrangement occurred in certain 3-(arylthio)-indoles to 2-(2-aminophenyl)benzothiophenes. 3-

(Arylthio)indoles **220**, in which the aryl group is an electron-rich system, underwent a novel structural rearrangement[112] to (aminophenyl)benzothiophenes **221** [$R^2R^3 = 6,7$-4,5-CH:CHCH:CH] on heating in polyphosphoric acid.

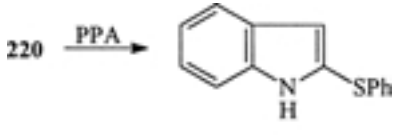


220 **221**

R = H; R^1 = 1-, 2-naphthyl, 3-$MeOC_6H_4$, 2,5-$Me_2C_6H_3$-
R = Me; R^1 = 2-naphthyl
R^2,R^3 = (6,7-; 4,5-CH:CHCH:CH).

SCHEME 118

Under these conditions, 3-(phenylthio)indole rearranged to 2-(phenylthio)-indole and not to 2-(aminophenyl)benzothiophenene.

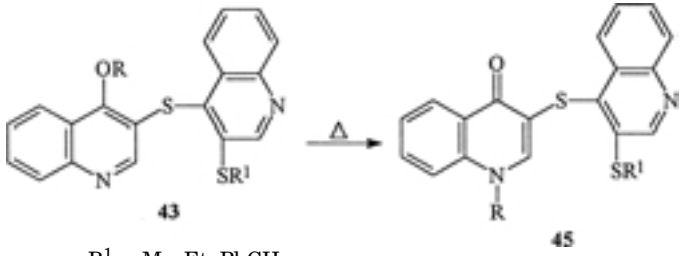


222

SCHEME 119

(ii) Thermal Rearrangement

Alkoxy (alkylthio)diquinolinylsulfides **43** underwent thermal rearrangement[113] to give oxodiquinolinyl sulfides **45**.



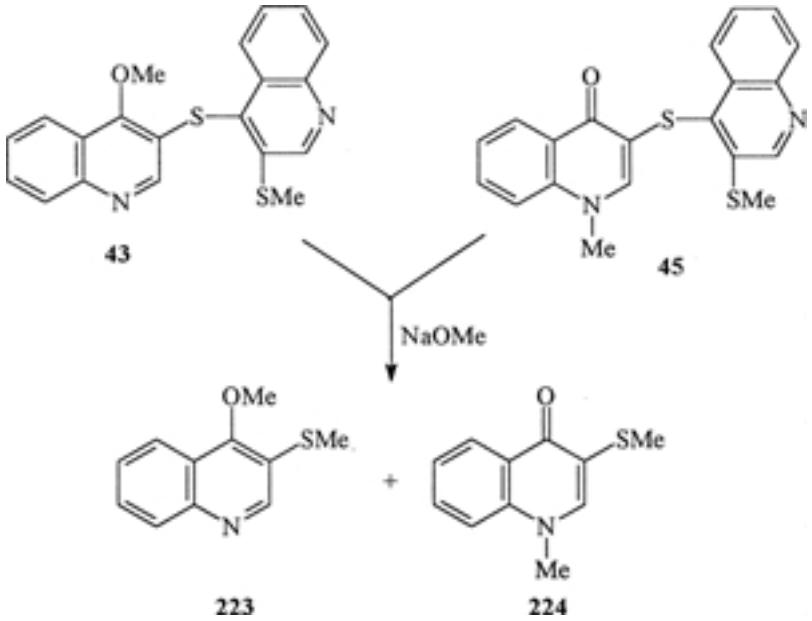
43 **45**

R = Me R^1 = Me, Et, $PhCH_2$
R = Et, $PhCH_2$ R^1 = Me

SCHEME 120

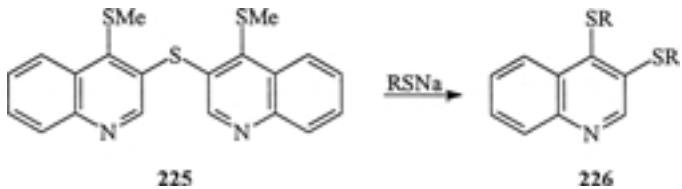
c. Cleavage

The reactions of 3,4′-diquinolinylsulfides **43** and **45** with sodium methoxide proceeded with the cleavage of the 4-quinolinyl-sulfur bond,[114] yielding 4-methoxy-3-(methylthio)quinoline (**223**) and quinolinone **224**, respectively.



SCHEME 121

Compound **225** (4,4′-methylthio-3,3′-diquinolinyl sulfide) reacted with S-nucleophiles (sodium alkanethiolates)[115a] with cleavage of C_3-quinolinyl-S, C_4-quinolinyl-S and CH_3—S bonds to form 3,4-dialkylthioquinolines **226** as the main products.

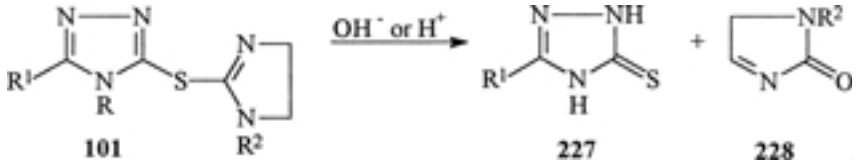


SCHEME 122

In the case of relatively bulky S-nucleophiles (2-methyl-2-propanethiolate and to some extent the ethane thiolate anion), the cleavage of the C_3-quinolinyl-S by a vicarious nucleophile (the

methane thiolate anion, liberated in the cleavage of the C_4-quinolinyl-S bond) was observed.

Triazolylimidazolinyl sulfides[52] **101** decomposed to 5-substituted-1,2,4-triazole-3-thiones **227** and imidazolidin-2-one **228** in an alkaline or acid medium.

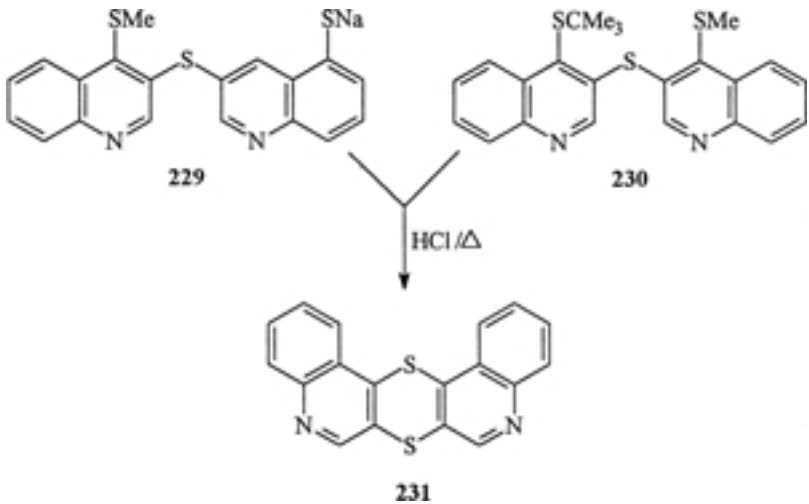


R = H, NH_2
R^1 = Ph, 4-pyridyl, pyrazolinyl, 3,5-$(MeO)_2C_6H_3$; R^2 = H

SCHEME 123

d. Cyclization

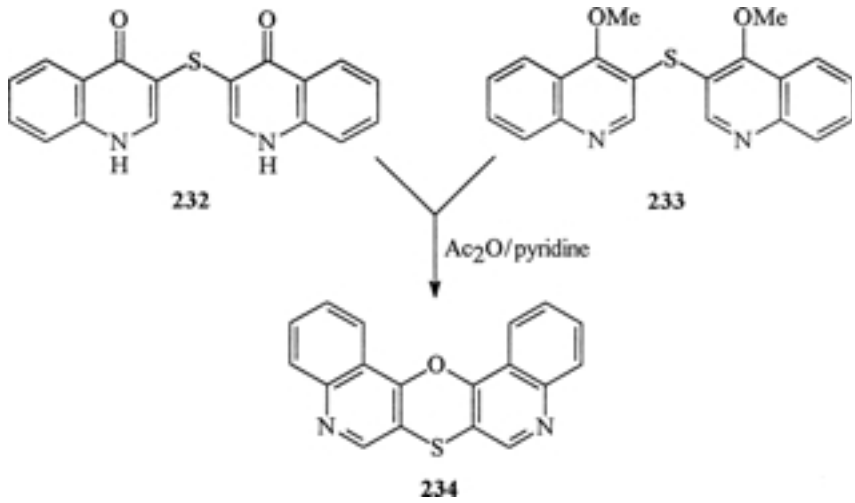
Sodium quinolinethiolate **229** or the diquinolinyl sulfide **230** gave isothioquinanthrene[115b] **231** by heating with hydrochloric acid.



SCHEME 124

Sulfides **232** and **233** with Ac_2O and pyridine[115c] underwent a ring-closure to oxathiin **234**.

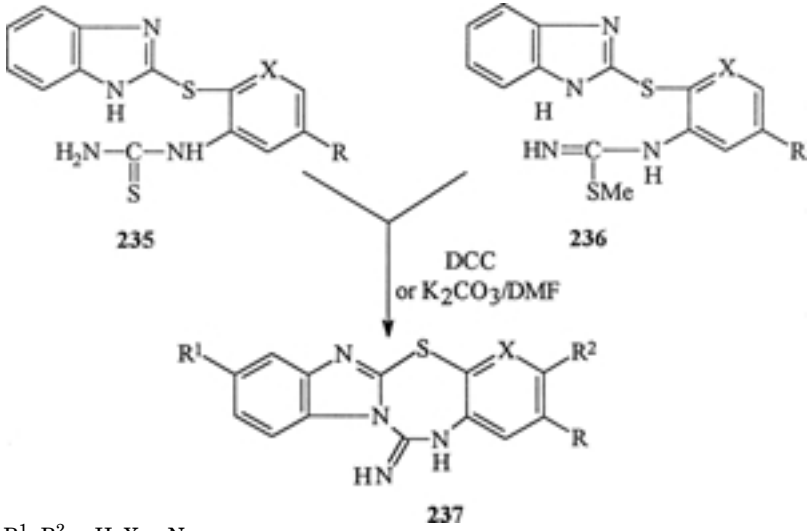
The cyclization of the *N*-substituted thiourea **235** or *N*-substituted-S-methylthiourea **236** derivatives, in the presence of DCC or



SCHEME 125

in potassium carbonate in DMF,[116a,b] gave new benzimidazo[2,1-*b*][1,3,5]benzo(pyrido)thiadiazepine derivatives **237.**

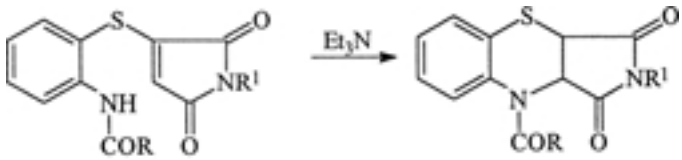
N-substituted-2[(2-acylaminophenyl)thio]maleimides **238** under went. Michael-type intramolecular cyclizations[117] when treated with a



R, R^1, R^2 = H; X = N
R = H, Cl, MeO, F_3C; R^2 = H, Cl; R^1 = H, Me; X = CH

SCHEME 126

weak base such as Et_3N to give 4-acyl-2,3-dihydro-1,4-benzothiazine-2,3-dicarboximides **239**.

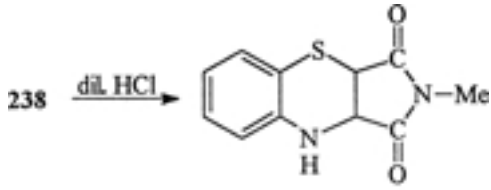


238 **239**

R = Me; R^1 = Me, Et, Ph, Ch_2Ph
R = Ph, Ch_2 Br; R^1 = Me

SCHEME 127

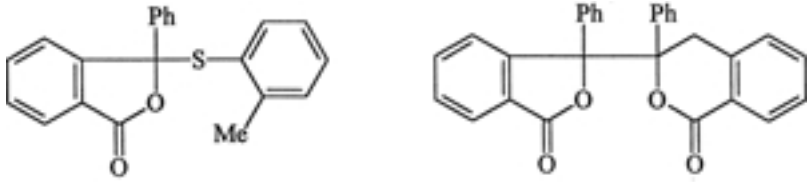
The treatment of compound **238** (R = R^1 = Me) with dil. HCl gave 2,3-dihydro-1,4-benzothiazine-2,3-dicarboximide (**240**).[117]



240

SCHEME 128

The photocyclization reaction of S-aryl-2-benzoylbenzothioates[118] to 3-aryl-3-(arylthio)isobenzofuranones **241** upon direct irradiation was accompanied by a subsequent homolytic cleavage reaction of the isobenzofuranone leading to dimers (±) and meso **242**. A stepwise mechanism involving (i) intramolecular cyclization to a zwitterionic intermediate and (ii) subsequent aryl migration occurred.



241 **242**

SCHEME 129

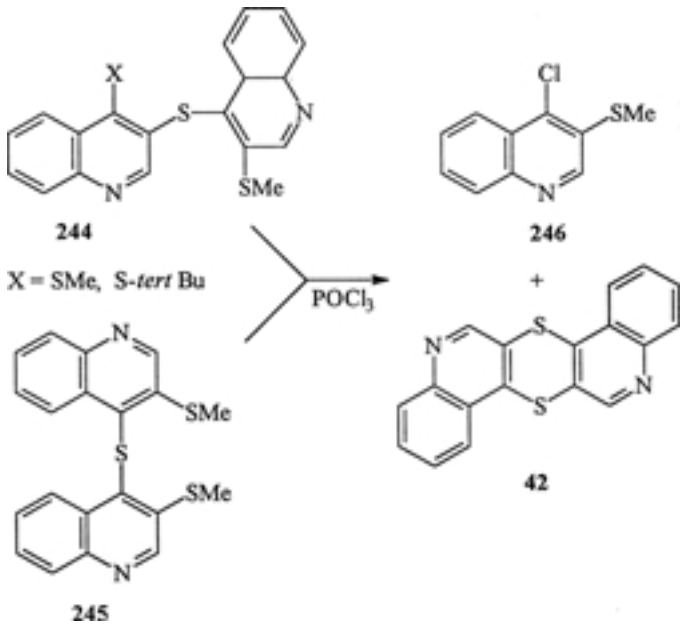
Dipyrimidinyl sulfide **38** was acylated at the amino group and subjected to cyclization[22] to **243** by treatment with base.

(R, R^1 = equiv. or different C_{1-4} alkoxy or di-C_1-C_4 alkylamina)

SCHEME 130

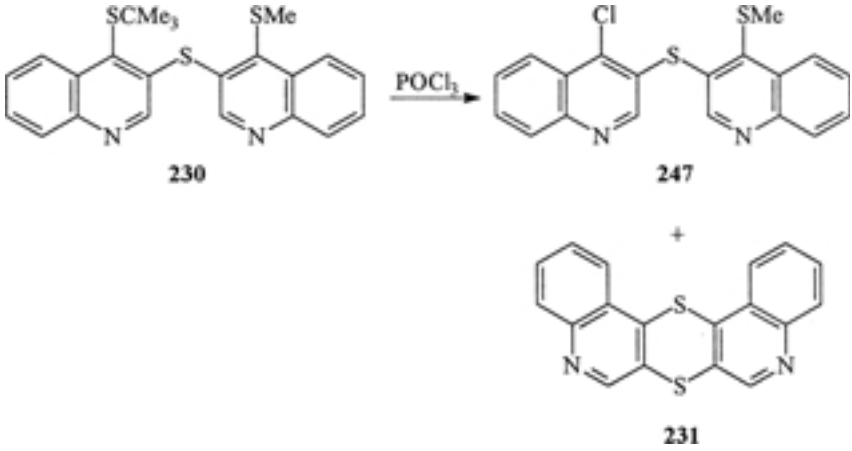
e. Chlorination

Chlorination of 3,4′-quinolinyl-bis-sulfide with phosphoryl chloride[26b,119] (alone or in *N*,*N*-dimethylformamide and ethanol) depended on the structure of the substrate. Three types of 4-chloroquinolines **246–248** were investigated. In the cases of 3,4′- and 4,4′-diquinolinyl sulfides, the cleavage of the C_4-quinolinyl-SR bond was observed regardless if the R was a 3- or 4-quinolinyl substituent. 4-chloroquinoline **246** was the main product, and thioquinanthrene **42** was the second product.



SCHEME 131

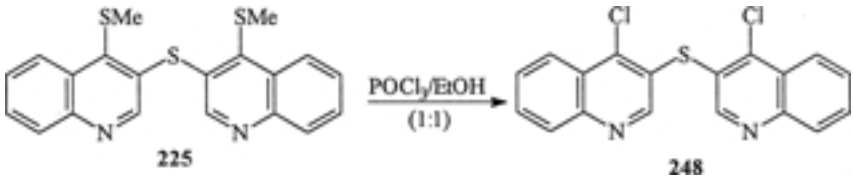
In the case of 3,3′-diquinolinyl sulfides, not only cleavage of the C_4-quinolinyl-SR (R=CMe_3) to give 4-chloroquinoline occurred but also cyclization to isothioquinanthrene[26b,119] **231** was observed.



230 **247** **231**

SCHEME 132

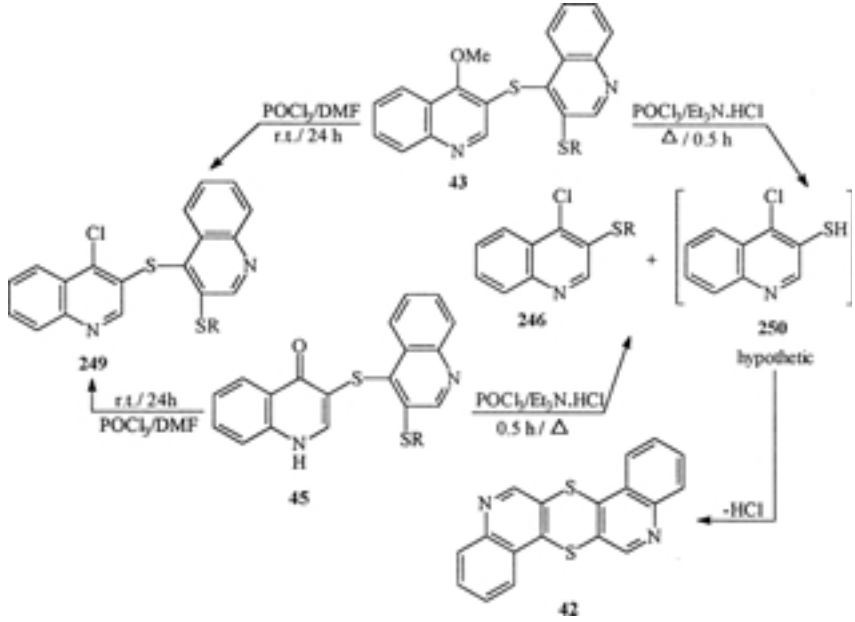
Sulfide **225** could be hydrolyzed easily by the mixture of hydrochloric acid-ethanol[26b,118] (1:1). Next, the oxo-group fuctions were readily transformed into the chlorine atom in the reaction with phosphoryl chloride and EtOH (1:1) to give the desired dichloroquinolinyl sulfide **248**.



225 **248**

SCHEME 133

The treatment of 4-methoxy-3′-alkylthio-3,4′-diquinolinyl sulfides **43** and 1,4-dihydro-4-oxo-3′-alkylthio-3,4′-diquinolinyl sulfides **45** with phosphoryl chloride[26b,119] as a chlorine source under mild conditions in DMF at r.t. allowed for the simple direct replacement of the 4-alkoxy or 4-oxogroup by the 4-chloro atom. Under more rigorous conditions, in the boiling phosphoryl chloride/triethylamine hydrochloride system, the replacement mentioned took place also but the reaction of **43** and **45** resulted in the cleavage of both γ-quinolinyl-heteroatom bonds and led to 4′-chloro-3-(alkylthio)quinoline and thioquinanthrene.



R = Ch_3: C_2H_5, $PhCH_2$

SCHEME 134

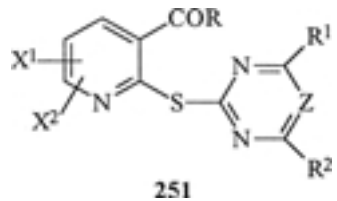
BIOLOGICAL ACTIVITIES OF SULFIDES

The importance of sulfides find their widest clinical application in the therapy of functional diseases are useful as herbicides, agrochemical fungicides, and antiinflammatory agents. According to Rout, Padhi, and Das, the fungicidal activity of many heterocyclic organosulfur compounds may be attributed to the presence of an N—C—S linkage as found in thiazoline and thiazolidinone.[120] On the other hand, dipyridyl sulfides are useful as bactericides, fungicides, and herbicides.[121]

A pyridine derivative **251** and its salt achieved an excellent herbicidal effect[122] on annual and perennial weeds growing in paddy fields and upland fields at a very small dosage. The derivatives are safe to rice, wheat, cotton, and corn and can be suitably applied as a herbicide to a field where these plants are cultivated.

Phenylthiopyrimidine, derivatives **252** showed 100% herbicidal effect for xanthium pensylvanicum, setaria faberii, Abutilon theophrasi, and Amaranthuslividus.[123]

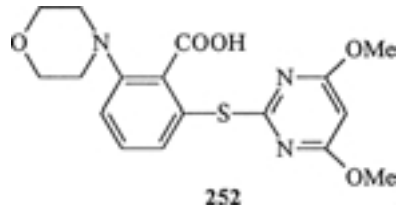
Nitromethylphenylthiopyrimidine derivatives **253** acted as herbicides or plant regulators and gave very good activity against *Echinochloa crus-galli* and *Amaranthus retroflexus*.[124]



251

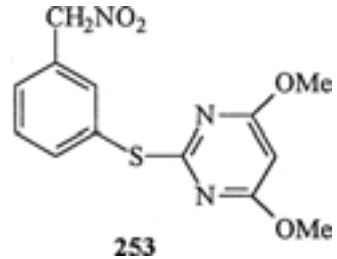
R = H, OH, alkoxy, alkoxyl alkoxy and derivatives.
R^1,R^2 = may be the same or different and are H, alkoxy, halogen, alkylamino, dialkylamino
X^1,X^2 = acylamino, cycloalkyl, alkoxyoxy, alknyloxy, a halogen-substituted alkoxy group, alkoxycarbonyl, an alkylamino, dialkylamino, Ph group
Z = CH, N

SCHEME 135



252

SCHEME 136



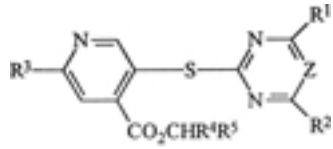
253

SCHEME 137

2-(2-pyrimidinylthio)picolinate derivatives and 2-(2-triazinylthio) picolinate derivatives **254** were prepared as herbicides and plant growth regulators.[124]

Compound **255** controlled 100% 5 weeds,[126] e.g., *Digitaria sp.*, *setaria viridis*, *chenopodium album*, and *Echinochloa crus-galli* but inflicted damage to corn, beet, rapeseed, and wheat.

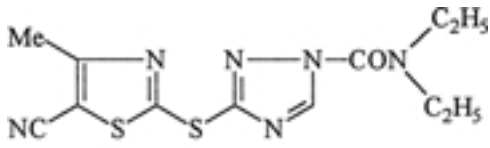
Thirty-nine sym. and unsym. dipyridyl sulfides[4] **256–258** substituted in the ring showed tuberculostatic activity against *Mycobacterium tuberculois*, *M. Kansasii*, *M. avium*, and *M. Fortuitum.*



254

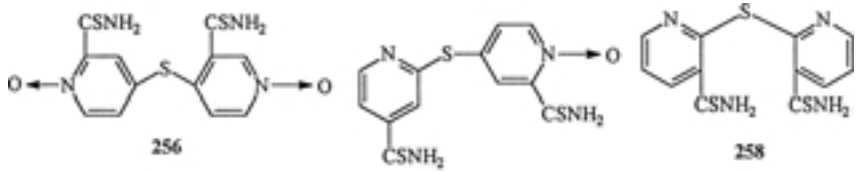
R^1,R^2 = (halo)alkyl, (halo)alkoxy, alkylthio
R^3 = H, OH, CN, NO_2, halo, alkyl R^4 = H, alkyl
R^5 = CR^6 = NOR^7, (un)substituted-5-membered heteroaryl, isoxazolinyl
R^6 = (un) substituted alkyl, Ph
R^7 = (un) substituted (cyclo) alkyl, alkenyl,
Z = N, CH

SCHEME 138



255

SCHEME 139



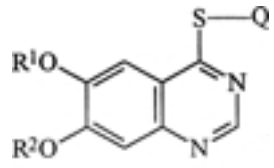
256 257 258

SCHEME 140

Quinoline and quinazoline derivatives **259** inhibit the platelet-derived growth factor receptor autophosphorylation and are useful in the treatment of certain cancers and arthritis.[127]

Sulfide **260** and its salt inhibited the effects of VEGF,[128] a property of value in the treatment of a number of disease states including cancer and rheumatoid arthritis.

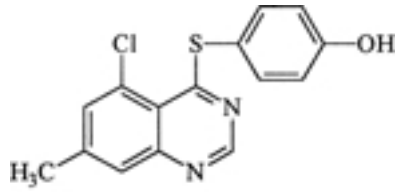
Compound **261** is used in the manufacture of medicaments for production of an antiangiogenic and/or a vascular permeability reducing effect. The agent also inhibits also the effect of VEGF,[129] a property useful in the treatment of a number of disease states inculding cancer and rheumatoid arthritis.



259

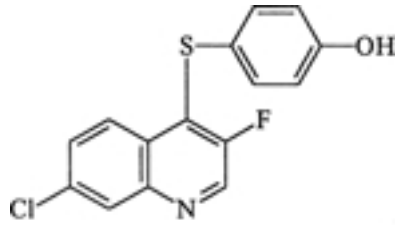
R^1,R^2 = H of C_1-C_4 alkyl or R^1 and R^2 together form C_1 to C_3 alkylene.
Q = substitued aryl or substituted heteroaryl.
W = CH, N.

SCHEME 141



260

SCHEME 142

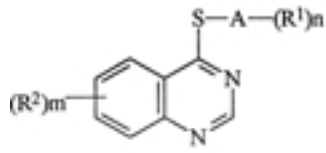


261

SCHEME 143

On the other hand, quinoline derivatives **262** were prepared for use in the production of an antiangiogenic and/or vascular permeability-reducing effect in warm-blooded animals.[130] The pharmaceutically acceptable salts inhibited the effects of VEGF, a property of value in the treatment of a number of disease states including cancer and rheumatoid arthritis.

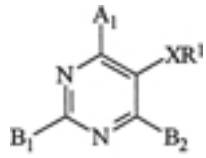
The pyrimidine derivatives **263** have potent interaction with central nervous system receptors, such as dopamine D_3 receptor or serotonin 5-HT_2[131] receptors, are excellent in absorbability in vivo, and are stable. Therefore, they are highly useful as a psychotropic drugs with a relief side effects.



262

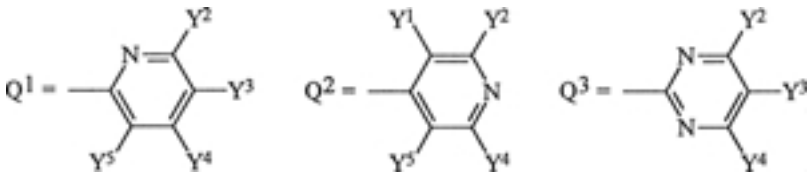
A = 8-, 9- 10-, 12-, or 13-membered bicyclic or tricyclic ring containing 1–3 O, N, and/or S heteroatoms
n = 0-5, m = 0-3
R^2 = H, OH, halo, CN, NO_2, CF_3, Alkyl(sulfanyl), alkoxy

SCHEME 144



263

A^1 = halo, substituted lower alkyl, subtituted cycloalkyl.
B_1B_2 = H substitued amino, X = S
R1 = $Q^1 - Q^3$



Y^1, Y^2, Y^3, Y^4, Y^5 = H, halo, substitued lower alkyl, substitudcycloalkyl, substituted loweralkenyl, substituted lower alkynyl, substituted aryl or substituted heterocyclyl

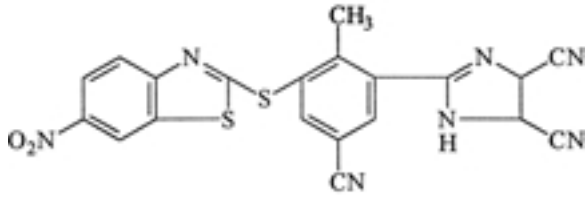
SCHEME 145

The activity of **264** is against insects and representatives of the order Acarina[132] that are harmful to animals and plants as well as against helminths in warm-blooded animals.

(4-isothiazolin-3-one-5-ylthio)benzothiazole (**105**) act as microbicides and inhibit *Aspergillus niger* and *Staphylococcus aureus*[54] with MTC.

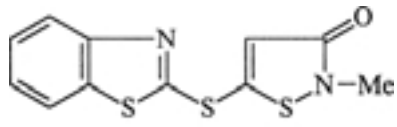
Bis(3-chloro-1,2,4-thiadiazol-5-yl)sulfide (**113**) was used as an agricultural fungicide and gave 100% control of *Pyricularia oryzae* on rice.[59]

3-hydroxy-4-methoxycarbonyl-1-methyl-5-phenylthio-1H-pyrrole (**265**) possesses fungicidal activity[133] against *Erisiphe graminis* and *Puccinia recondita*.



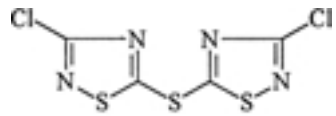
264

SCHEME 146



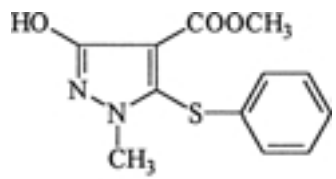
105

SCHEME 147



113

SCHEME 148

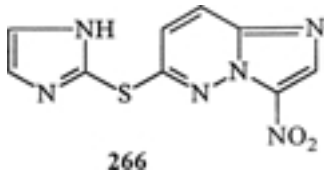


265

SCHEME 149

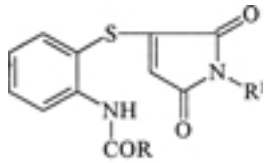
Nitroimidazole compounds were disclosed as antibacterial agents and antiulcer agents.[134] Thus, 7-[(1H-imidazol-2-yl)thio]-2-nitroimidazo-[1,2-*b*]-pyridazine (**266**) was claimed to be effective against *Heliobacterium pylori* (*campylobacter pyloridis*).

N-substituted-2[(2-acylaminophenyl)thio]maleimides **238** exhibited good antibacterial activity[117] against Gram-positive bacteria such as *Bacillus subtilis* and *Staphylococcus aureus.*



266

SCHEME 150

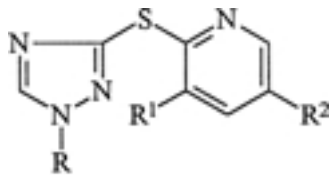


238

R = Me; R^1 = Me; Er; Ph; $PhCH_2$
R = Ph; Ch_2Br; R^1 = Me

SCHEME 151

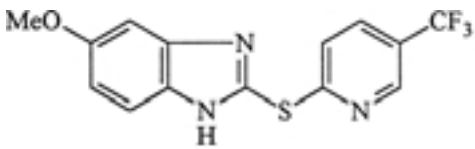
Compounds **67** (R = H, Me; R^1 = H; R^2 = NO_2) had a powerful action on platelet aggregation.[40] These agents were thought to inhibit platelet aggregation via an inhibition of the cyclooxygenase-peroxides complex (PGS complex), preventing synthesis of prostaglandins.



67

SCHEME 152

On the other hand, mercaptobenzimidazole **65′** inhibited gastric juice secretion in rats.[38]

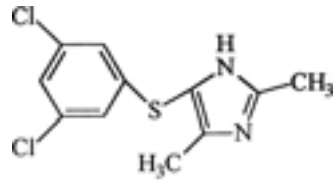


65′

SCHEME 153

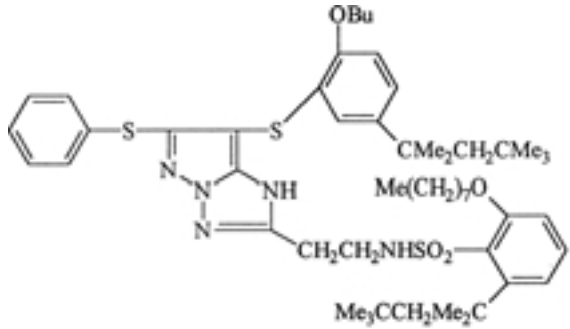
Imidazole derivatives **267** have the effect of specifically inhibiting the growth of HIV as a pathogenic virus and is low in toxicity.[135]

Compound **268** was used as a photographic magenta coupler.[90]



267

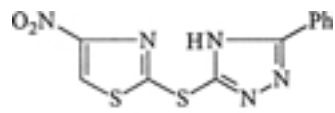
SCHEME 154



268

SCHEME 155

Compound **95** was active as protein tyrosine enzyme-related cellular signal transduction modulators.[49]



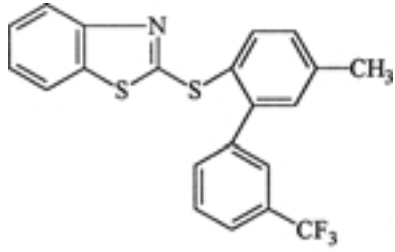
95

SCHEME 156

Phenylthiobenzothiazole derivatives **269** showed 90–100% control against *Sesbania exaltata, Abutilon theophrasti, Solanum sp.*, and *Viola sp.*[136]

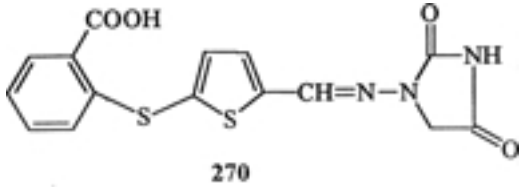
2-(5-substituted-2-thienylthio)benzoic acid derivatives **270** were screened for their muscle relaxant and parasympatholytic activities.[97b]

Compound **271** is a psychotropic drug having a patent affinity for the D_4 receptor but no affinity for the $\alpha 1$ receptor and is useful as a remedy for mental symptoms of schizophrenia, periodic psychosis, Parkinson's disease, drug abuse, or those accompanying senile dementia or Alzheimer's disease.[137]



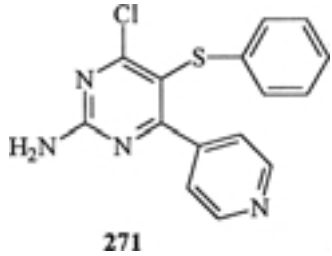
269

SCHEME 157



270

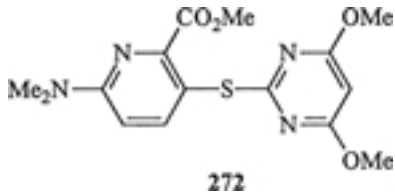
SCHEME 158



271

SCHEME 159

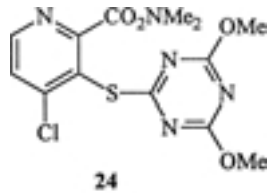
Pyrimidinylthio picolinate[11] derivative **272** effected 100% kill against *Cyperus difformis*.



272

SCHEME 160

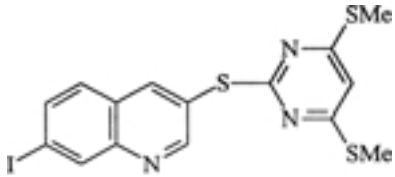
Triazinylthiopyridine derivative[12] **24** almost completely killed tall morning glory and completely killed radish.



24

SCHEME 161

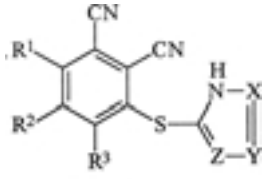
3-(2-pyrimidinylthio) quinoline derivatives **41** controlled 100% *Sphaerotheca fuliginea* in cucumber seedlings.[23]



41

SCHEME 162

Thermochromic compounds 3-[(heteroarylthio)]-1,2-benzenedicarbonitriles **273** are suitable for use as active components in thermal information recording systems,[138] specially for laser-optical information recording media, e.g., 3-(1*H*-imidazol-2-ylthio)-1,2-benzenedicarbonitrile.



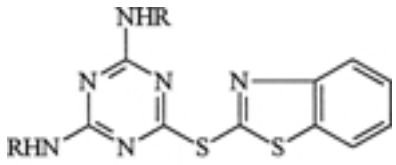
273

R^1 - R^3 = H, alkyl X, Y, Z = methine or N

SCHEME 163

2,4-diarylamino-6-(benzothiazol-2-ylthio)-s-triazines **76** were evaluated for antimicrobial as well as antitubercular activity.[43] Some were found to possess moderate antimicrobial activity as compared to saturated drugs, while only one compound showed antibubercular activity.

N-[2,3-dihydro-1-oxo-6-[(2-thiazolyl)thio]-1*H*-inden-5-yl] methane sulfonamide[139] (**274**) is useful for the treatment of cyclooxygenase-mediated diseases such as pain, fever, and inflammation of a variety

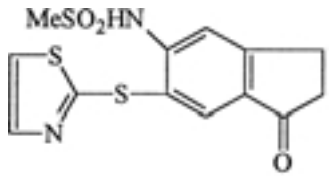


76

R = substituted Ph

SCHEME 164

of conditions including rheumatic fever, symptoms associated with influenza or other viral infections, the common cold, low back and neck pain, dysmenorrhea, headache, toothache, sprains and strains, myositis, neuralgia synovitis, arthritis, including rheumatoid arthritis degenerative joint diseases (osteoarthirtis), gout, and ankylosing spondylitis, bursitis and burns.



274

SCHEME 165

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